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THE TREATMENT OF CHRONIC ULCERATIVE COLITIS

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Results of Conservative Therapy

ALTHOUGH most patients with chronic ulcerative colitis do well without operation, about 20 per cent suffer from severe and intractable forms of the disease and do not improve on medical treatment. Many of these persons die of the disease or are incapacitated, both economically and socially. Since colectomy rehabilitates these patients and prevents most of the fatal complications of the disease, serious consideration must be given to extending the indications for surgical intervention.

Prior to the development of the modern type of ileostomy appliance, the life of the patient who had undergone an ileostomy was not a pleasant one. The appliances were not leakproof, many were malodorous, and provision was not made for protecting the skin from the irritating discharges of the ileostomy. Moreover, the technic and postoperative management of ileostomy and of colectomy had not been developed, the mortality rate was high among surgical patients, and often the stomas were so placed that they could not be fitted with a satisfactory appliance. For these reasons, gastroenterologists in the past seldom advised ileostomy or colectomy for patients with ulcerative colitis.

Results of Simultaneous Ileostomy and Subtotal Colectomy in the Treatment of Chronic Ulcerative Colitis

In the past 5 years advances in the technic of ileostomy and colectomy and improvements in the preoperative and postoperative care of patients with ulcerative colitis have resulted in a striking reduction in both morbidity and mortality after operation. For example, in the past 2 years (September 1949—September 1951) we have performed subtotal colectomy with simultaneous ileostomy 22 times as an elective procedure for chronic ulcerative colitis and removed the lower sigmoid colon and rectal stump as a secondary operation in 27 cases without a fatality. Rehabilitation of the patient occurred promptly after removal of the colon as exemplified by one patient who gained 30 pounds in the first 30 days, and no patient has failed to make a satisfactory social adjustment following the ileostomy.

Results of Conservative Treatment of Acute Toxic Ulcerative Colitis

The most dangerous type of ulcerative colitis is the rare acute, toxic variety which constitutes only 5 per cent of all cases of ulcerative colitis. Toxicity may be the first manifestation of the disease or may be an exacerbation of a chronic

colitis. In either case, the mortality rate is exceedingly high either following ileostomy alone or with conventional medical treatment.[1,2]

The true mortality rate in patients with acute toxic ulcerative colitis has not always been appreciated, because many of these patients are discharged from the hospital improved only to die at home as a result of an acute exacerbation of the disease. Thus, although only 36 per cent[2] of the patients with acute toxic ulcerative colitis died at the time of the first hospitalization, we found that, by the time 2 to 5 years had passed, the mortality had risen to 68 per cent, and little difference was apparent in the over-all mortality whether the patients had been treated by ileostomy or by conservative measures. Moreover only 13 per cent of the patients receiving medical treatment were rehabilitated socially and economically.

Rationale of Subtotal Colectomy with Simultaneous Ileostomy in Acute Toxic Ulcerative Colitis

Frequently the statement has been made that a patient with acute toxic ulcerative colitis is too ill to withstand ileostomy. Often this statement is correct because, when the strain of anesthetic and operation and the inevitable disturbances of nutrition and electrolyte balance which accompany ileostomy are superimposed on the anemia, sepsis, and metabolic exhaustion from which the patient is already suffering, the result may be fatal. But if at the same time it is possible to remove the colon which is the source of the anemia and sepsis, the patient has a better chance of withstanding operation and recovering good health. Our attitude toward the patient with acute toxic ulcerative colitis, therefore, has undergone an "about face," and we no longer say that a patient is too sick to be operated upon; rather we agree with Ferguson[3] who said "the patients are too sick **not** to be operated upon."

The operation which is performed for patients with acute toxic ulcerative colitis should not be the minimal operation of ileostomy, which may cause the least shock and which also results in the least improvement, but should be the maximum operation of subtotal colectomy with ileostomy, which causes prompt improvement in the general condition of the patient. It is important to remember that patients with acute toxic ulcerative colitis do not often die as a result of their operations but as a result of their disease. Even extensive operations are tolerated well provided that the disease is eradicated.

Patients with primary acute toxic ulcerative colitis often have colons that are atonic and distended due to the invasion and destruction of both mucosal and muscular coats of the bowel (fig. 1). This distention is a grave prognostic sign and often signifies impending perforation. These colons are, in effect, nothing more than a serosal sac filled with feces, pus and blood and lined only with shaggy ulcers interspersed by ragged mucosa. The physiologic effect of such a colon is comparable to that of an extensive third degree burn covered with a fecal poultice. After colectomy the patient's recovery from the effects of sepsis is often as prompt and dramatic as the recovery which follows the cleansing and grafting of a badly infected third degree burn of comparable area (fig. 2).

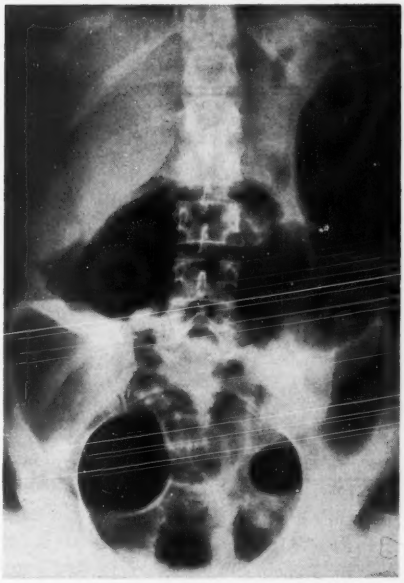

FIG. 1. Toxic fulminating ulcerative colitis. Flat film of abdomen showing dilatation of colon at height of toxicity.

Until the colon is removed, there is a continuous loss of blood and protein into the lumen of the bowel and a continuous absorption of its toxic contents. Pronounced inflammatory changes are present, blood vessels are thrombosed, and there is necrosis of mucosa with deep ulceration associated with multiple localized areas of peritonitis. Unless the bowel is removed, the ulceration may progress to perforation and fatal peritonitis.

In acute toxic colitis, ileostomy alone does little more than slightly retard this process (fig. 3). After ileostomy, fever, toxemia, bacteremia and a tendency to develop thromboembolic phenomena may persist. When the colon is removed, however, the source of these difficulties is eradicated; the blood and serum protein loss is checked, fever and toxemia subside and the serum proteins rise rapidly. Evidence of vitamin deficiency disappears, cutaneous ulcers heal and arthritis subsides. All of these results tend to occur with dramatic suddenness after colectomy, whereas after ileostomy alone there may be little or no alteration in the clinical picture, or the improvement may be so slow that it must be measured in weeks or months instead of days.

Results of Subtotal Colectomy with Simultaneous Ileostomy in Acute Toxic Ulcerative Colitis

During the past 2 years (September 1949—September 1951) we have performed 10 ileostomies with simultaneous subtotal colectomies in the treatment

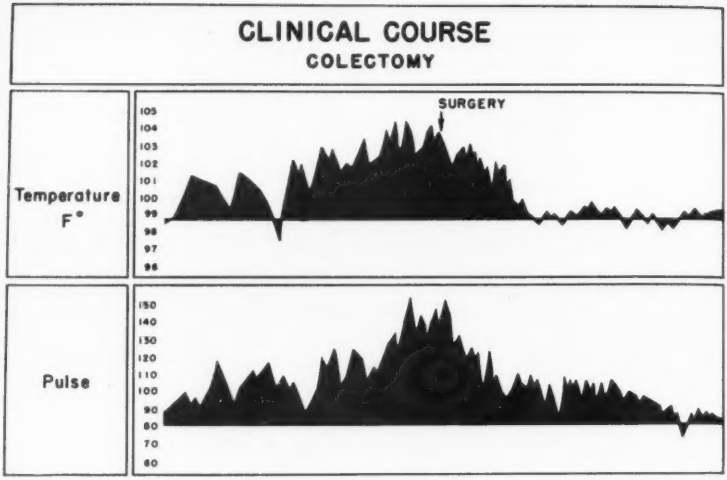

FIG. 2

of all patients in whom the diagnosis of acute toxic ulcerative colitis was made. Operation was not withheld because of the seriousness of the disease or the patient's poor condition. The 2 patients who died were moribund at the time of operation. One (aged 62) had had numerous perforations of the colon and the other was in the terminal stages of toxemia with massive edema and a serum albumin of 0.6 mg. per cent. The other patients in this series have improved satisfactorily.

The median day of discharge was the thirteenth postoperative day, a noteworthy advancement when compared with the former method of treatment in which ileostomy followed by a stage colectomy required an average of 2 months hospitalization with many months of convalescent care at home between stages. The patients subjected to ileostomy and simultaneous colectomy are now completely rehabilitated and have returned to their former economic and social activities. Several patients were able to return to work within a few weeks subsequent to operation.

Although sufficient time has not yet elapsed to enable us to evaluate the mortality rate over a 5 year period, there is no reason to believe that these patients are any longer in grave danger of dying as a result of their disease. Since the mortality in a similar group of patients managed by more conservative means was 60 per cent, and since by medical treatment we had been able to rehabilitate economically and socially only 13 per cent of the patients of this particular group, it is apparent that simultaneous ileostomy with colectomy is both safer and more effective than conservative measures, including ileostomy alone.

Relationship of Chronic Ulcerative Colitis to Carcinoma of the Colon

Many patients with longstanding ulcerative colitis whose colons are not removed develop highly malignant carcinomas of the colon. In Gleckler's and Brown's[4] series, reported from this clinic, carcinoma was found in nearly 10 per cent of the patients with ulcerative colitis who were subjected to colectomy and, in 4 of the 12 cases reported, the carcinoma developed after ileostomy had been performed. It is, therefore, apparent that ileostomy alone does not protect against the development of cancer, and that this fatal complication is a definite menace to patients who have protracted ulcerative colitis.

Discussion

If the ileostomy is properly made and placed, the modern type of ileostomy appliance fits snugly without leakage and the skin is not irritated by the ileal content. We have invariably left the rectum in place at the time of the subtotal colectomy and have told the patients that, should a medical cure for ulcerative colitis be found, the continuity of the intestinal tract could be re-established; however no patient in this consecutive series of 32 cases has complained of the ileostomy or requested re-establishment of intestinal continuity. After the patients are adjusted following an ileostomy, the possibility of a carcinoma developing in the rectal stump is explained to them and they usually will permit removal of the rectum although recognizing the fact that the ileostomy becomes permanent.

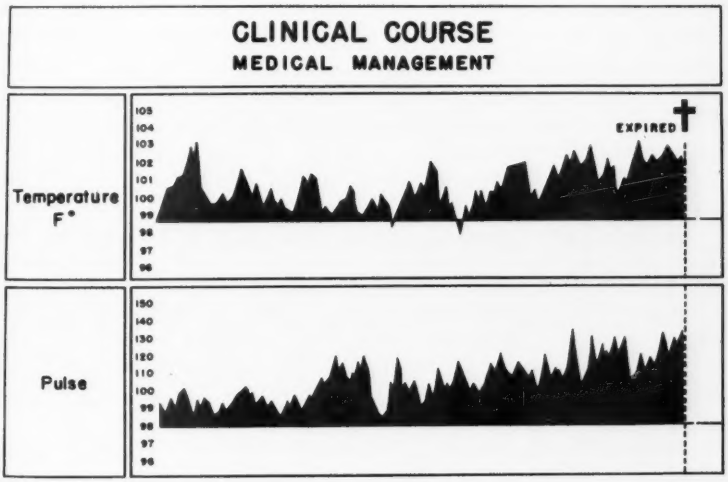

FIG. 3

Since multiple stage operations for ulcerative colitis are complicated by contamination from the ileostomy and the exteriorized stump of the colon, they are attended by a higher incidence of wound infection and postoperative morbidity than a one stage procedure. Multiple stage operations require several times as much hospitalization as the single stage procedure. The patient's recovery from the disease and his return to normal social and economic life are much more rapid following simultaneous ileostomy and colectomy than following stage operations.

Although economic factors are important, the main consideration is saving the patient's life. The danger in the toxic form of colitis is not from the operation but from the disease, and the sooner the patient's disease is eradicated the safer he becomes. For these reasons we believe that one stage ileostomy and colectomy is the preferred treatment for acute toxic ulcerative colitis.

Cortisone and ACTH have been used in ulcerative colitis and appear to benefit the patient symptomatically as long as they are given. It is possible that these agents may be of some value in preparing desperately ill patients for operation. In one case in this series the improvement was striking and operation appeared to be made more safe by its use. In a second case, however, no benefit was observed and, in a third not included in this series in which no operation was performed because the diagnosis of ulcerative colitis was not made before autopsy, a fatal perforation followed the use of cortisone. Since similar experience has been reported by others we do not believe that these agents should be used except in the immediate preoperative period in an attempt to ameliorate the condition of desperately ill patients. Although milder forms of the disease should be given a trial on conventional medical treatment, removal of the colon as completely and as quickly as possible appears to be the safest method of treating patients with acute toxic or severe chronic ulcerative colitis. We do not believe that ileostomy alone is indicated in the treatment of this disease.

Summary

1. Prolonged conservative treatment of intractable ulcerative colitis is both dangerous and unsatisfactory.

2. The mortality rate from cancer of the colon developing in patients with intractable ulcerative colitis exceeds the risk of colectomy.

3. One stage colectomy with simultaneous ileostomy is the safest and most effective treatment for acute toxic ulcerative colitis, or for the severe intractable chronic forms of the disease.

4. There is no place for ileostomy alone in the treatment of ulcerative colitis.

5. In acute toxic ulcerative colitis, the mortality rate among patients having one stage ileostomies and colectomies is only one-third that of those receiving medical treatment or having ileostomies alone.

6. In chronic, nontoxic forms of ulcerative colitis, there has been no mortality in a consecutive series of 22 elective one stage ileostomies and colectomies followed in most cases by removal of the rectal stump.

7. Since a properly made and placed ileostomy fitted with a modern type of appliance enables the patients to make satisfactory social and economic adjustments, there is no longer any reason to deny the benefits of one stage ileostomy and colectomy to those whose lives are threatened or whose social and economic activities are limited by ulcerative colitis.

References

1. Brown, C. H., Gleckler, W. J. and Jones, T. E.: Surgical treatment of chronic nonspecific ulcerative colitis. Gastroenterology **14**:465 (April) 1950.

2. Crile, George, Jr. and Thomas, C. Y.: Treatment of acute toxic ulcerative colitis. Gastroenterology (In press).

3. Ferguson, L. K. and Stevens, L. W.: Surgery of complications of ulcerative colitis. Gastroenterology **11**:640 (Nov.) 1948.

4. Gleckler, W. J. and Brown, C. H.: Carcinoma of colon complicating chronic ulcerative colitis. Gastroenterology **14**:455 (April) 1950.

BRAIN TUMOR IN INFANCY

Report of Case With Four-Year Follow-up After Surgical Removal

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ALTHOUGH tumors of the brain are encountered with moderate frequency during childhood, their occurrence during the first year of life is distinctly rare. Stern[1] found 62 intracranial tumors in children under the age of 12 at 2808 consecutive autopsies at the Great Ormond Hospital; of these, 6 occurred during the first year of life. Critchley[2] reported 125 brain tumors in children under the age of 16 among a total of 1028 cases of brain tumor; only 1 of these occurred in an infant under the age of one year. Cushing,[3] in a series of 1108 verified intracranial tumors, found 24 in children younger than 5 years; one of these proved to be a teratoma in an infant 2 months of age. Gross[4] reviewed the literature concerning tumors of the brain during the first 2 years of life, citing 9 cases which had been reported from 1861 to 1931; to these he added 9 cases which he had observed in the same age group. In a series of 100 intracranial tumors occurring in children under 15 years of age, Smith and Fincher[5] encountered none during the first year of life. In a review of the literature of cases of brain tumor occurring during the neonatal period (the first 60 days of life) Arnstein et al[6] found 13 reports of such lesions prior to June 1950 and added a case of angioma of the choroid plexus in a 3 day old infant. Bailey et al[7] in their complete monograph reviewed a series of 100 cases in children younger than 16 years of age; of these, 5 occurred during the first year of life and 7 during the second year. No reference will be made to the many interesting papers in which small numbers of cases in early childhood have been reported; most of them are cited in the bibliographies or reference lists of the authors mentioned.

In childhood, gliomas predominate over other types of brain tumor (75 per cent) and occur most frequently in the subtentorial region. Among the gliomas in this age group, the astrocytoma and the medulloblastoma are the more common. The rarity of meningeal tumors in childhood is notable, and this is particularly true in infancy. Bailey and Ingraham[8] reported 3 cases of intracranial fibrosarcoma of the dura, one in an infant 27 days old. It seems possible that their case 3 may have been a benign meningioma of fibroblastic type.

Brain tumors during the first year of life usually are not recognized before death and autopsy, since the clinical picture is most likely to lead to a diagnosis of congenital hydrocephalus. The following case report will illustrate some of the difficulties of diagnosis. Fortunately the tumor which was encountered in this baby proved to be a meningioma of fibroblastic type, and the growth shows no signs of recurrence 4 years after its surgical removal.

Case Report

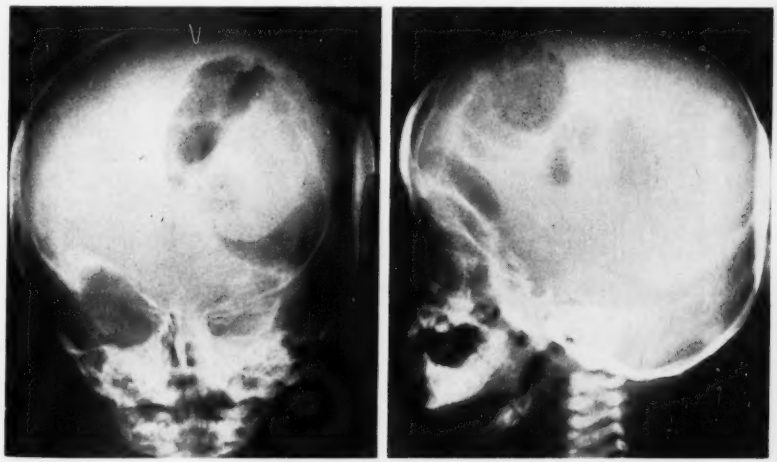
A baby boy, 6 months old, was brought to the Clinic by his parents on January 20, 1947 because of an enlarged head and spasms. He was the fourth child of the mother and apparently had been normal at birth. His siblings were normal children and had shown normal development. At the age of 3 months the patient began to experience involuntary muscular contractions in which the legs became stiff, the arms flexed, and the eyes rolled. Since that time the parents had noticed progressive enlargement of the baby's head.

Examination revealed a large head, whose circumference was 50 cm., a small face, a bulging anterior fontanel, and widely separated skull sutures. There was no demonstrable evidence of paralysis of the arms or legs. Ophthalmoscopic examination showed 2 or 3 diopters of papilledema in both eyes.

Roentgenograms of the skull showed enormous enlargement. As measured on the films, the anteroposterior diameter was 17 cm. and the vertical diameter 16.5 cm. The sella turcica showed no erosion. The bones of the skull were thin and the anterior fontanel was enlarged. No calcifications were visible. There was moderate asymmetry of the skull in the posteroanterior projection, the left side being slightly larger than the right side. The superior orbital margins were indistinct, especially on the left side, and the orbits appeared to be somewhat more widely separated than normal.

A diagnosis of congenital hydrocephalus was made, and it was suggested to the parents that the baby be admitted to the hospital for further studies and possible excision of the choroid plexuses, although the prognosis in any event appeared distinctly unfavorable.

The infant was admitted to the hospital on January 29, 1947. On the following day a needle was inserted through the scalp at the left angle of the anterior fontanel and



(a) (b)

FIG. 1. Roentgenograms after intracranial injection of air on left side showing bizarre bubble formation. Lower mass of air in anteroposterior view suggests outline of inferior surface of tumor.

presumably into a dilated left ventricle. Fifty cc. of yellow fluid was aspirated and coagulated in the test tube. The fluid contained 140 lymphocytes per cu. mm., a heavy trace of globulin, and 3300 mg. of total protein per 100 cc. Lumbar puncture was then performed and clear colorless cerebrospinal fluid was obtained. The lumbar fluid contained 6 cells and 297 mg. of total protein. The following day the right angle of the anterior fontanel was punctured and at a depth of 7.5 cm. clear, colorless fluid was encountered, presumably in the right ventricle. The fluid from the right side contained only 2 cells per cu. mm. and only 155 mg. of total protein. These studies caused us to abandon the diagnosis of congenital hydrocephalus, inasmuch as the yellow fluid with its high protein content suggested the presence of organic disease, either inflammatory or neoplastic, in the left side of the brain. On February 6, 1947 an attempt was made to gain further information by ventriculography; 30 cc. of air was injected into the left side of the head through the anterior fontanel after removing a small quantity of yellow fluid. The roentgenograms demonstrated loculated collections of air, probably bubbles, scattered throughout the parietal, temporal, and frontal regions on the left side (fig. 1). There was no air on the right side of the head. No definite diagnosis could be made from these films, but the possibility of cystic changes or neoplasm in the left cerebral hemisphere was considered.

Operation was advised, and on February 11, 1947 a scalp flap was turned down in the left parietal area and a disk of bone about 1.5 inches in diameter was removed with scissors. When the dura was opened, a thin-walled transparent cyst bulged through the opening. Numerous blood vessels coursed in the wall of the cyst. The cyst was opened and 30 cc. of clear yellow fluid was removed by aspiration. Through the opening in the skull, brain tissue could be seen in the posterior part of the cranial cavity on the left side. The anterior half of the left cerebral hemisphere appeared to be atrophic or compressed by the encysted fluid and by a large, firm, encapsulated tumor. This growth seemed to be rather closely attached to the dura underlying the coronal suture on the left side. The posterior aspect of the tumor was gradully exposed by cotton dissection

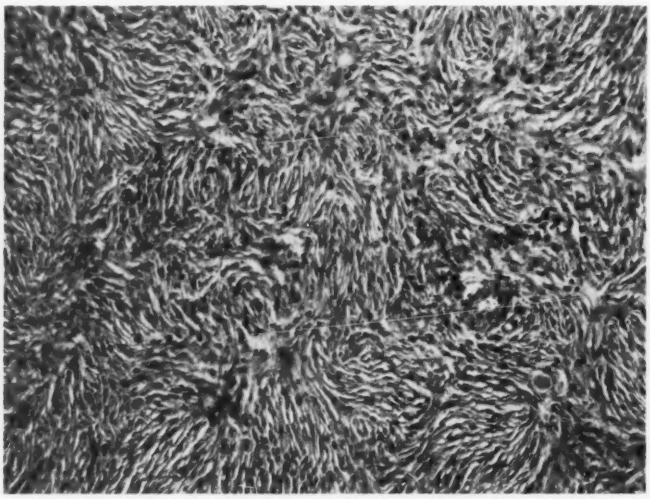


FIG. 2. Photomicrograph of fibroblastic meningioma which was removed in this case (x70).

FIG. 3. Patient 3½ years after operation.

and approximately two-thirds of it was removed by means of the electric loop. The tumor was exceptionally hard and avascular, and its cut surface was white in color. The portion of the tumor which was not removed at this operation appeared to extend forward into the frontal part of the cranial cavity on the left side. Because of the baby's age, and the duration of the operation, it was considered wise to postpone further removal of the tumor until a later date. The dura was partially closed with nylon sutures, the bone disk was replaced and anchored with nylon sutures, and the scalp incision was closed.

On February 22, 1947 the surgical wound was opened and the remaining portion of the tumor was removed. Its attachment to the dura underlying the coronal suture was divided with the electric knife. The lateral aspect of the tumor was encapsulated, but its medial aspect appeared to be more intimately associated with brain tissue of the left cerebral hemisphere. All of the hard tumor tissue was removed, and it is probable that small portions of cerebral tissue were removed with it. At the end of the procedure the left cerebral hemisphere was found to be atrophic, its surface lying 2 inches below the inner table of the skull. The dura was then loosely closed, and the bone disk replaced and anchored at four points with nylon sutures. The scalp was closed with interrupted nylon sutures.

The baby developed a low-grade postoperative staphylococcic meningitis which fortunately responded well to penicillin, and he was afebrile for a week before discharge from the hospital on March 19, 1947.

The microscopic appearance of the tumor was described by Dr. John B Hazard, Cleveland Clinic Pathologist, as follows: "The mass is formed by slender spindle-shaped cells arranged in short interlacing bundles. Nuclei are elongated or oval and appear well differentiated. In some of the marginal zones, the tissue is somewhat more cellular; in one section the spindle-shaped cells extend into cerebral tissue. Invading tumor cells encase patches of glial tissue in this area. In addition to the spindle-shaped cells, there are some plump cells of moderate size with abundant pink cytoplasm and with somewhat vesicular nuclei. A PTAH stain shows fine collagen bundles between these spindle-

shaped cells. No mitoses are apparent. Pathologic diagnosis: "Meningioma, fibroblastic type, apparently slowly growing" (fig. 2).

The child has been examined at intervals since operation for a period of more than 4 years, the latest observation occurring on August 2, 1951. At that time his mother stated that he had been well and had experienced no convulsions. He had begun to talk at the age of 2½ years and to walk at the age of 3 years. Examination showed the boy to be in good general condition, but with a persistent right hemiparesis. He walked with a circumduction type of gait. Although his speech was limited, he was able to name objects and to use many simple words. There was no papilledema. An electroencephalogram showed abnormal delta waves from the left frontal and parietal areas. Measures were instituted for rehabilitation of the right arm and leg. His parents plan to have him start school in September 1952. (Fig. 3).

Discussion

A review of the literature and of the case presented above makes it clear that intracranial tumors in infancy are not only rare but difficult to diagnose before death or operation. In the vast majority of cases a rapid increase in the size of an infant's head is due, not to the presence of a tumor, but rather to so-called "congenital hydrocephalus." The latter condition may be the result of stenosis of the aqueduct, nonpatency of the foramina of Luschka and Magendie, the Arnold-Chiari malformation, inadequate absorption of cerebrospinal fluid in the cortical subarachnoid pathways, or other causes. Nevertheless, the possibility of intracranial tumor should be borne in mind when an infant exhibits a rapidly enlarging head, convulsions, and vomiting. Aspiration of xanthochromic fluid from one side of the cranial cavity through the bulging anterior fontanel should cause one to suspect tumor, particularly if the fluid is found to contain a large quantity of protein. Air studies may be of some assistance. Finally, of course, the presence of a tumor can be determined only by operation or by necropsy. Occasionally a surgical effort may be rewarded by the discovery and removal of a benign neoplasm, as in the case reported.

References

1. Stern, R. O.: Cerebral tumors in children; pathological report. Arch. Dis. Childhood **12**:291 (Oct.) 1937.
2. Critchley, M.: Brain tumors in children; their general symptomatology. Brit. J. Child. Dis. **22**:251 (Oct.-Dec.) 1925.
3. Cushing, H.: Intracranial tumors of preadolescence. Am. J. Dis. Child. **33**:551 (April) 1927.
4. Gross, S. W.: Tumors of brain in infancy; clinical and pathologic study. Am. J. Dis. Child. **48**:739 (Oct.) 1934.
5. Smith, W. A. and Fincher, E. F.: Intracranial tumors in children; preliminary study of 100 cases. South. M. J. **35**:547 (June) 1942.
6. Arnstein, L. H., Boldrey, E. and Naffziger, H. C.: Case report and survey of brain tumors during neonatal period. J. Neurosurg. **8**:315 (May) 1951.
7. Bailey, P., Buchanan, D. N. and Bucy, P. C.: Intracranial Tumors of Infancy and Childhood. Chicago, University of Chicago Press, 1939.
8. Bailey, O. T. and Ingraham, F. D.: Intracranial fibrosarcomas of dura mater in childhood; pathological characteristics and surgical management. J. Neurosurg. **2**:1 (Jan.) 1945.

OBSTRUCTIVE BILIARY CIRRHOSIS WITH ASCITES

Report of Two Cases

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BILIARY cirrhosis has long been of interest in clinical and experimental medicine. Karsner[1] has classified biliary cirrhosis into two main categories, the first resulting from extrahepatic obstruction of the large bile ducts and the second caused by intrahepatic obstruction of the finer bile channels. The important feature in Karsner's classification is that the changes in the liver parenchyma are brought about by obstruction of the bile flow, whether the obstruction lies outside the liver in the large bile ducts or within the liver in finer biliary channels. Both give signs of obstructive jaundice when examined by liver function tests and bile circulation studies. This is in contradistinction to Laennec's cirrhosis or hepatitis, diseases primarily effecting the parenchymal cell of the liver. In the present discussion, we are concerned only with the liver changes caused by obstruction in the large extrahepatic bile ducts.

Experimentally, changes typical of biliary cirrhosis have been produced in animals. Rous and Larimore[2] reported that ligation of the common duct in rabbits resulted in cirrhosis of an interlobular type with many new bile ducts, simple atrophy of the parenchyma of the liver, and a dwindling in the size of the lobule. By ligation of smaller ducts they were able to produce a pure monolobular cirrhosis. They reported similar changes in the dog. Cameron and Oakley[3] found that occlusion of the common bile duct in rats, guinea pigs, and rabbits resulted in comparable findings with bile duct hyperplasia, dilatation of the bile passages, the growth of new bile ducts, atrophy, and degeneration and regeneration of liver cells. They observed "hyaline" degeneration of liver cell columns. MacMahon, Lawrence and Maddock[4] studied the changes in the liver of guinea pigs, induced by ligation of the common bile duct. They state, "In the early stages, bile stasis, necrosis and regeneration of individual liver cells, edema, and infiltration of the portal areas are the most prominent features. Later there is an apparent increase in the number of bile ducts; the portal connective tissue is increased." Stewart and Lieber[5] reported smilar observations produced by ligation of the common duct of the cat, and noted a remarkable parallelism between the results of this experiment and the lesions seen clinically in man. It is obvious from investigative work that obstruction to bile flow results in profound and usually characteristic changes in the liver.

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Alterations associated clinically with complete or intermittent and partial occlusion of the common bile duct also have been reported. MacMahon and Mallory[6] studied 20 cases of obstructive cirrhosis in adults and 10 in children and found changes similar to those observed in the experimental animal. They stated: "The early stage in all cases is characterized by a dilatation of the ducts with bile stasis within the lobule. This is followed by an elongation of the terminal ducts associated with an appreciable increase in portal connective tissue, commonly accompanied with a moderate cellular infiltration into the portal areas and the appearance of regressive changes in the liver cells in the central zones of the lobule." Lieber and Stewart[7] discussed the changes caused by obstruction to the common bile duct by carcinoma of the pancreas; they reported that the biliary conducting system undergoes a tremendous volumetric increase, the process extending to the small branches. The canaliculi are distended with bile thrombi, and bile pigment may be present in the cells of the central portion of the lobule. Degenerative and necrotic changes involving the hepatic cells about the central vein may occur. The intrahepatic ducts elongate and become tortuous. They found a characteristic and pronounced deposition of connective tissue which is interlobular, intralobular and even perilobular. Gibson and Robertson[8] found similar changes in 21 of 244 patients having died of obstructive jaundice. The characteristic features again were moderate to intense increase in portal connective tissue with intralobular extension, evidence of parenchymal degeneration, bile thrombi, an increase in interlobular bile ducts, and collections of lymphocytes or polymorphonuclear leukocytes. They emphasized the presence of parenchymal degeneration and regeneration and fibrosis. In none of these patients did the past history suggest antecedent liver disease, and these authors attributed the changes in the liver to obstruction of the bile flow. From a clinical viewpoint, obstruction to the bile flow can cause profound changes in the liver.

Ascites, when coexistent in any form of cirrhosis, is always considered a late sign and evidence of severe fibrosis and portal hypertension. Its presence, however, is particularly infrequent in biliary cirrhosis. Hanot, in his original description of intrahepatic biliary cirrhosis, did not include ascites as one of the findings. More recently, Dauphinee and Sinclair[9] reported 4 patients with intrahepatic biliary cirrhosis and ascites. MacMahon and Mallory,[6] in reviewing 30 cases of extrahepatic obstructive biliary cirrhosis, described one ascitic patient. Gibson and Robertson,[8] in their series of 244 cases of obstructive jaundice, found 6 patients with concomitant ascites; one of these had carcinomatosis of the peritoneum. Snell, Greene, and Rowntree[10] described ascites, extensive collateral circulation, and monolobular hepatic fibrosis in 2 dogs, occurring after prolonged ligation of the common duct. Ascites is relatively frequent in patients with Laennec's cirrhosis and in severe hepatitis. Conversely, it infrequently accompanies obstructive jaundice and extrahepatic biliary cirrhosis; its presence may considerably confuse the clinical picture and make the correct diagnosis difficult. The 2 patients subsequently reported, who had extrahepatic obstructive cirrhosis associated with ascites, were of unusual clinical interest.

Case Reports

Case 1. A 69 year old woman was admitted to the hospital in November 1950 with a history of swelling of the abdomen apparently for 3 weeks, jaundice for 4 weeks, and repeated attacks of chills and fever occurring every 3 weeks and lasting 1 to 2 days for the previous 6 months. Severe pruritus, light stools and dark urine had been present since the onset of jaundice. She had lost 38 pounds in the past 15 months. She had been observed at the Clinic in November 1949, at which time she complained of mild indigestion. Complete physical examination, laboratory studies and gastrointestinal roentgenologic examination were all entirely negative except for nonfilling of the gallbladder. She was seen again in May 1950. She had lost a little weight but was otherwise apparently well. Her past history was noncontributory.

On physical examination in November she was emaciated and icteric. The liver was enlarged 7 to 8 cm. in the midclavicular line and the abdomen was distended; a fluid wave and shifting dullness were present. Laboratory examinations were as follows: Blood count normal. Urine was positive for bile, as were the stools. Alkaline phosphatase was 26.5, serum bilirubin 8.0 with a direct reaction; the cephalin cholesterol flocculation test was negative, and the thymol turbidity was 2.0. Serum albumin was 3.1 and globulin 2.9.

A paracentesis was performed and 1300 cc. of ascitic fluid was removed; this was studied for tumor cells but none were found. Roentgenologic examination of the stomach and colon were negative except for the presence of a large duodenal diverticulum. During the next few days, the patient's icteric index fluctuated between 25 and 40 and the stools were intermittently negative for bile. A needle biopsy of the liver was obtained, using the Vim-Silverman needle, and the specimen showed definite bile stasis and severe biliary cirrhosis (fig. 1).

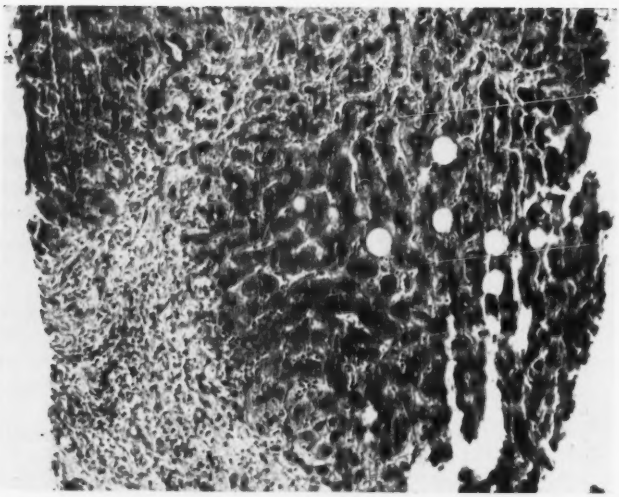
An exploration was performed on the fourteenth day to establish the cause of the obstruction and to relieve it. The gallbladder and common duct were found to be greatly dilated and thickened and a large calculus was palpated in the ampula of Vater. The liver was finely nodular and the spleen moderately enlarged with a dilated splenic vein. The calculus was removed and a cholangiogram of the patient on the operating table showed no additional stones. A T-tube was left in the common duct.

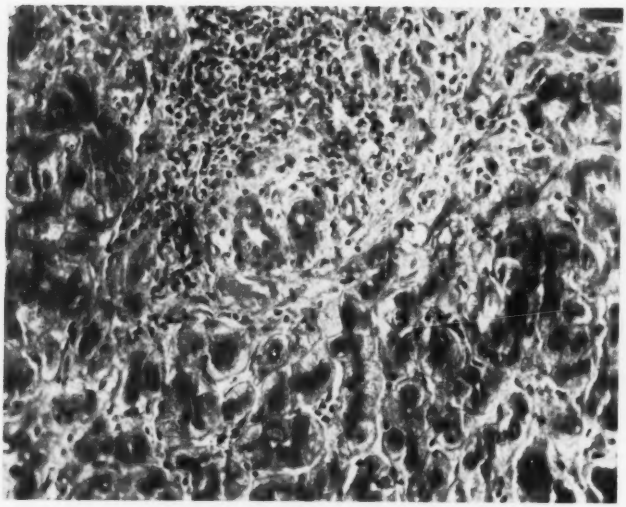
Following surgery, the patient's jaundice rapidly subsided and her postoperative course was uneventful. Two months subsequent to operation she was neither jaundiced, nor ascitic; a cholangiogram still showed some dilatation of the common duct, but no evidence of obstruction. Another cholangiogram taken 2 months later revealed no change in the patient's condition and the T-tube was removed. At that time her icteric index was 6, and 3 per cent retention of the bromsulfalein dye was present in 30 minutes (5 mg. of dye per kilo body weight). She was last examined on May 23, at which time she was symptom-free and had gained 39 pounds. There was no evidence of jaundice or ascites. The liver edge was barely palpable at the costal margin. Liver function studies were entirely normal. Bromsulfalein liver function test showed 4 per cent retention of the dye in 30 minutes, the cephalin flocculation test was negative, the thymol turbidity was 2.0; the alkaline phosphatase was now 5 units, serum albumin was 4.3 and globulin 3.0.

Comment

This patient presented a complicated diagnostic problem, and surgery was recommended only after lengthy consideration of her condition. The previous observation of a nonfunctioning gallbladder, the history of chills and fever,

(a)





(b)

FIG. 1. Needle biopsy of the liver in case 1 (common duct stone). (a) Increase in the connective tissue in the portal areas; some increase in number of bile ducts. The fibrosis is fairly sharply demarcated, and the liver cells appear relatively well preserved with little distortion of the liver columns themselves (x100). (b) Portal fibrosis is evident, and there is some increase in bile ducts. There is an infiltration of lymphocytes present; this has been reported in common duct ligation in animals but is uncommon in man (x200).

and the evidence from laboratory studies were all suggestive of partial obstruction of the common duct. The fluctuating icteric index, elevated alkaline phosphatase, the intermittent appearance of bile in the stool, negative cephalin flocculation and thymol turbidity tests were all compatible with partial biliary obstruction, and a preoperative diagnosis of a common duct stone was made. The presence of ascites was confusing as this condition infrequently accompanies obstructive jaundice, even when complicated by biliary cirrhosis. The surgeon declined to operate, as he believed the ascites indicated severe Laennec's cirrhosis. Our results[11] on liver biopsy have previously been recorded and this experience proved most helpful in diagnosing the case. The needle biopsy specimen showed severe bile stasis and biliary cirrhosis. On the basis of this evidence the surgeon was persuaded to operate. Otherwise the patient's condition necessarily would have been treated as Laennec's cirrhosis, with an inevitably fatal outcome. This case illustrates the fact that needle biopsy of the liver may be extremely useful in the diagnosis of obscure liver disease, and in differentiating obstructive from hepatic jaundice.

This case also shows, as have the experimental and clinical studies already cited, that partial obstruction of the common bile duct can cause profound changes in the liver, and in this instance ascites. While seldom associated with obstructive jaundice, ascites may be produced by the severe changes in the liver and the biliary cirrhosis which develop secondary to the biliary obstruc-

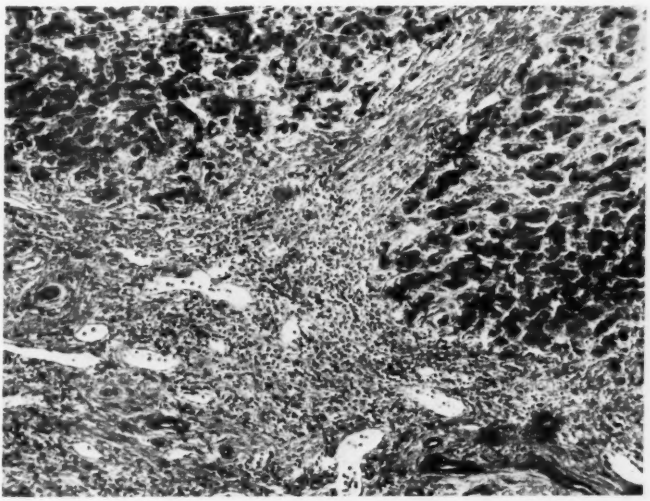


Fig. 2. Section of liver; autopsy specimen; carcinoma of the common bile duct. Portal fibrosis with increase in bile ducts is evident. There is extension of the fibrosis perilobularly, and also between the liver columns. The latter is unusual in biliary cirrhosis and probably occurred because of the long duration of obstruction. Many bile thrombi were present (x70).

tion. One should not hastily diagnose hepatic jaundice (Laennec's cirrhosis or hepatitis) because of the presence of ascites. Infrequently it may be a manifestation of severe biliary cirrhosis due, secondarily, to obstruction of the common bile duct.

Of further interest is the fact that, once the obstruction in the common bile duct was relieved, the jaundice and ascites rapidly disappeared. Remarkable improvement in biliary cirrhosis in experimental animals has also been reported when the obstruction in the common bile duct is removed. A good prognosis, as illustrated by this case, can be given patients with severe biliary cirrhosis, if that cirrhosis is caused by obstruction of the common bile duct and the obstruction is surgically relieved.

Case 2. A 39 year old woman was first seen in the Clinic in April 1942 with a history of a cholecystectomy performed in 1940, followed by a persistent fistula which necessitated an exploration of the common duct in July 1941. The fistula finally closed in November 1941. For a month prior to admission to the Clinic, jaundice, pruritus, clay-colored stools and periodic diarrhea had been present. Positive physical findings on admission were pronounced icterus, an enlargement of the left ventricle with a grade IV apical rumbling diastolic murmur and a grade III apical systolic murmur consistent with rheumatic heart disease. Laboratory examinations were essentially normal except for an icteric index of 75. At operation no common duct could be identified in the dense mass of adhesions, and a catheter was left in the stump of the hepatic ducts.

Following surgery the jaundice disappeared rapidly, but on the tenth postoperative day the patient vomited a large amount of blood. Her prothrombin time was 50 per cent of normal but returned to 100 per cent following two transfusions; she then made satisfactory progress. The stools became brown and the T-tube was removed in July, 2 months after surgery.

In December 1942 there was a recurrence of jaundice and clay-colored stools, and she was reoperated upon in an attempt to insert a vitallium tube in the hepatic ducts. However, the ducts were too small and another catheter was inserted. This measure relieved her jaundice until January 1944 when the jaundice recurred after the tube had pulled out. A new tube was inserted which, while it drained bile, never completely relieved her jaundice. In May 1945 she was readmitted because of bleeding about the tube, and physical examination for the first time showed enlargement of the liver and spleen. Her icteric index was 25. She was given several blood transfusions, and discharged on an outpatient basis. The patient was seen in 1946, 1947 and 1948 and reported occasional episodes of bleeding about the tube and mild fluctuating jaundice. In June 1948 there were several occurrences of chills and fever associated with fluctuating jaundice and clay-colored stools.

Because of loss of weight and repeated episodes of chills and fever which accompanied the jaundice, she was again admitted to the hospital in November 1949. Physical examination once more showed enlargement of the liver and spleen and, for the first time, ascites. At operation, in addition to massive adhesions, the liver was found to be finely nodular and the spleen greatly enlarged. At this time a tube was connected to the stump of the hepatic duct and through the duodenum. Postoperatively the jaundice subsided and the patient progressed satisfactorily. An x-ray of the stomach revealed a small gastric ulcer on the lesser curvature.

In March 1950 her icteric index was 68, serum albumin was 2.5 and globulin 4.7. The thymol turbidity was elevated to 7 units and the cephalin cholesterol flocculation test 4 plus. The patient was seen again in September 1950 at which time the jaundice

and ascites had increased, and she had developed edema of the legs. There was little or no pulmonary congestion, but digitalis was administered and a low salt diet prescribed. The peripheral edema subsided but there was no diminution of the ascites.

In December 1950 the patient was admitted for the last time because of recurrence of jaundice and edema of the legs. Physical examination revealed pronounced icterus, noticeable enlargement of the liver and spleen, and moderate ascites, but no evidence of pulmonary congestion. The icteric index was 100, thymol 5.5. units, and prothrombin time 68 per cent. Exploration was undertaken for the fourth time in the Cleveland Clinic Hospital and another polyethylene tube was inserted into a small hepatic duct that was observed to drain bile. On the sixth postoperative day she suddenly vomited a large quantity of blood, went into irrecoverable shock, and died.

Autopsy examination revealed multiple superficial gastric ulcerations as the cause of the massive gastrointestinal hemorrhage. The heart weighed 314 Gm. and showed stenosis of the mitral valve. The spleen weighed 800 Gm. and was soft and flabby. The liver, which weighed 1,500 Gm., was dark green in color, was finely granular and studded with unusually small nodules. Microscopic examination of the liver disclosed definite perilobular fibrosis with dense lymphocytic infiltration, proliferation of the bile ducts, and abundant green-brown pigment within the liver cells and sinusoids.

Comment

This case illustrates characteristically the protracted and usually fatal course of patients with stricture of the common duct. The circumstance is particularly unfortunate because it is possible that, had the initial surgery been uncomplicated and had cholangiography been employed at that time, she would have recovered from the biliary tract disease. Patients with strictures of the common duct, even when the obstruction is relieved by a vitallium tube or an anastomotic operation, are likely to develop repeated attacks of cholangitis and subsequently fatal biliary cirrhosis.

This case also emphasized the profound effect of obstruction of the common bile duct upon the liver. That the damage was severe is demonstrated by the enlargement of the liver and spleen, the development of ascites, the reversal of the albumin globulin ratio and the positive flocculation tests. The latter two developments indicate extreme damage to the parenchymal cells of the liver.

A third point of interest concerning this case is the fact that gastric ulceration was discovered almost 3 years prior to the death of the patient while focal gastric ulceration with hemorrhage was the immediate cause.

Markowitz[12] noted that, in animals, total exclusion of bile from the intestines was a common cause of typical chronic peptic ulcers.

Discussion

The development of ascites is rare in obstructive biliary cirrhosis and, as in portal cirrhosis, the mechanism is thought to be largely a combination of two factors, (1) portal hypertension, and (2) decreased plasma colloid osmotic pressure. Higgins et al[13] studied 19 patients with ascites in a series of 35 cases of chronic and subacute hepatitis, and found that ascites seldom was present when the colloidal osmotic pressure of the plasma remained within normal

limits. They assumed that the dependence of the formation of ascites on a low level of plasma proteins was a useful point in diagnosis. Ralli et al[14] observed a third factor in the formation of ascites when they demonstrated that the urine of effected patients had a greater antidiuretic effect when injected into hydrated rats than urine from nonascitic or normal persons. They believed that this blocking effect indicated failure of the liver to destroy some antidiuretic principle, probably secreted by the posterior pituitary gland. Whether or not a patient with liver disease develops ascites, may depend on the combination of these three factors.

The course of the 2 patients, one terminating in death and the other in recovery, demonstrates the importance of recognizing the presence of obstructive biliary cirrhosis and eliminating the causative factor. The significance of an accurate diagnosis cannot be overemphasized. White[15] suggested, after having reviewed 500 cases of jaundice, that surgery be avoided in cases of acute icterus with brown stools; thus the danger of operating on a patient with acute hepatitis will be eliminated. Although the usual mortality of gallbladder surgery is 2 to 5 per cent, his series showed 35 per cent in patients with cirrhosis and 100 per cent in patients with severe acute hepatitis who were subjected to operation. Surgery on a patient with Laennec's cirrhosis or with acute hepatitis may precipitate death, while lack of surgery in a patient with obstructive jaundice caused by a common duct stone, as in case 1, may be equally fatal. Liver biopsy, showing bile stasis and biliary cirrhosis as in case 1, may be of considerable help in the decision as to whether a patient with apparently obstructive jaundice should be subjected to operation.

Summary

Two unusual cases of obstructive biliary cirrhosis with ascites have been presented. In the first case, the biliary cirrhosis and ascites were secondary to a common duct stone, and the patient was cured following removal of the stone. Liver biopsy was especially helpful in the diagnosis and in the decision to operate. The second case was due to stricture of the common duct and illustrates the frequently relentless course and fatal termination in these patients despite repeated attempts at reconstruction of the common duct and re-establishment of biliary drainage. Both cases demonstrate the severe changes in the liver that can result from obstruction of the extrahepatic bile ducts.

References

1. Karsner, H. T.: Morphology and pathogenesis of hepatic cirrhosis. Am. J. Clin. Path. **13**:569 (Nov.) 1943.
2. Rous, P. and Larimore, L. D.: The biliary factor in liver lesions. J. Exper. M. **32**:249, 1920.
3. Cameron, G. R. and Oakley, C. L.: Ligation of common bile duct. J. Path. and Bact. **35**:769 (Sept.) 1932.
4. MacMahon, H. E., Lawrence, J. S. and Maddock, S. J.: Experimental obstructive cirrhosis. Am. J. Path. **5**:631 (Nov.) 1929.

5. Stewart, H. L. and Lieber, M. M.: Ligation of common bile duct in cat. Arch. Path. **19**:34 (Jan.) 1935.

6. MacMahon, H. E. and Mallory, F. B.: Obstructive cirrhosis. Am. J. Path. **5**:645 (Nov.) 1929.

7. Lieber, M. M. and Stewart, H. L.: Hepatic and bile duct changes from obstruction of common bile duct due to pancreatic carcinoma. Arch. Path. **17**:362 (March) 1934.

8. Gibson, W. R. and Robertson, H. E.: So-called biliary cirrhosis. Arch. Path. **28**:37 (July) 1939.

9. Dauphinee, J. A. and Sinclair, J. C.: Primary biliary cirrhosis. Canad. M.A.J. **61**:1 (July) 1949.

10. Snell, A. M., Greene, C. H. and Rowntree, L. G.: Diseases of liver; further studies in experimental obstructive jaundice. Arch. Int. Med. **40**:471 (Oct.) 1927.

11. Rossmiller, H. R., Brown, C. H. and Whitman, J. F.: Needle biopsy of liver. Cleveland Clin. Quart. **17**:64 (April) 1950.

12. Markowitz, J.: Experimental Surgery, ed. 2. Baltimore, Williams and Wilkins Company, 1949, p. 546.

13. Higgins, G., and others: Ascites in chronic disease of liver. Quart. J. Med. **16**:263 (Oct.) 1947.

14. Ralli, E. P., Robson, J. S., Clarke, D. H. and Hoagland, C. L.: Factors influencing ascites in patients with cirrhosis of liver. J. Clin. Investigation **24**:316 (May) 1945.

15. White, F. W.: Study of errors in diagnosis of jaundice. New England J. Med. **229**:997 (Dec. 30) 1943.

INTRACRANIAL EPENDYMOMA

Clinicopathologic Observations

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UNTIL recently, little has been added to our knowledge of the ependymal group of gliomas as first described by Bailey[1] in 1924. In the following year, Bailey[2] presented the results of the study of 5 cases designated as ependymoblastoma and 7 as ependymoma. These results originated the conception that the tumors were malignant primarily because of their predilection for the fourth ventricle, a site presenting surgical difficulties in the complete removal of such growths. Although the impression has persisted that ependymoblastomas grow more rapidly and are more malignant lesions than ependymomas, analysis of the first series reported by Bailey and Cushing[2] failed to corroborate this assumption. Also, Bailey later recognized the fact that, insofar as prognosis was concerned,[3] the difference between these tumors was minimal. His conclusion was emphasized further by Davidoff[3] and later by Mabon et al[4] and Penfield.[5]

Kernohan and Fletcher-Kernohan[6] in 1937 subdivided the ependymomas into the following subtypes: (1) epithelial, (2) cellular, (3) myxopapillary and (4) papillomas of the choroid plexus. This classification also included the neuroepithelioma of Bailey and Cushing in the general group of ependymomas. Although an attempt was made to correlate the prognosis with these individual subdivisions, the results were unsatisfactory. More recently (1949), Mabon, Svien, Kernohan and Craig[4] reviewed 57 cases of ependymoma in which the patients were operated upon, and graded the neoplasms according to pleomorphism of nuclei and cytoplasm, hyperchromatism, mitotic figures and preservation of architecture. They found a close correlation between the degrees of dedifferentiation of these gliomas and the survival periods of the patients. The results revealed survival rates to be inversely proportional to the degree of anaplasia or grade of the tumor.

The purpose of this study was to apply these same principles of gradation to a group of ependymal tumors seen at the Cleveland Clinic from 1933 to 1948. It was hoped that such an analysis would offer histologic criteria for the predictability of growth rate or prognosis.

Material

Thirteen cases of ependymoma which were referred to surgery were observed during the previously mentioned 15 year period. One additional case was

disregarded because the follow-up study was incomplete. The tissue was fixed in 10 per cent formalin or Zenker's fluid. All slides from each individual case were reviewed. The sections were stained with hematoxylin, eosin and methylene blue, Mallory's phosphotungstic acid hematoxylin and Masson's trichrome stain. Mitotic figures were noted and recorded as the number per twelve high power fields. Actually all fields available were studied for mitoses. The estimation of cellularity, stroma, and rosette formation was relative and was classified as 4 plus, 3 plus, 2 plus, 1 plus. Since the group was small, this method presented little difficulty. Coincident evaluations were obtained on four different occasions, and two observers independently agreed upon these designations. In regard to uniformity of cell cytoplasm, it was discovered that, for the most part, the cell outline was indefinite and this feature could not be estimated accurately. The occurrence of the nuclei in symplasmic masses in this type of tumor has not been stressed as a histologic feature. Because of this absence of well defined cell margins, pleomorphism must depend upon nuclear variation. A well differentiated growth demonstrated 75 per cent or more of the nuclei to be uniform. Moderate dedifferentiation was considered when 50 to 75 per cent of the nuclei appeared similar. Less than 50 per cent uniformity was considered to indicate marked dedifferentiation. The terms "rosette" and "pseudorosette" in this discussion are defined as follows: A true rosette is a cuff of cells arranged about a central space; the term pseudorosette is reserved for that structural arrangement of cells which surround a blood vessel or central mass of fine fibers. The histologic studies were performed prior to the tabulation of the clinical data to avoid undue subjective influence.

Results

Age and Sex. Of the 13 patients studied, 8 were women and 5 men. The mean age for the group at the time of operation was 19.3 years; the ages ranged from 2½ to 44 years.

Duration of Symptoms Prior to Surgery in Relationship to Survival (table 1). Inaccuracy is recognized in the evaluation of onset of symptoms, and amplified, perhaps, in analyzing the symptoms of brain tumor, viz., headache and nausea and vomiting, since many other illnesses can produce such episodes. The onset of symptoms accepted as indicative of brain tumor was established at the time when symptoms became either progressive or persistent. It is obviously impossible to estimate the duration of the lesion prior to onset so that the exact inception of a given neoplasm is not known. Using the previously described criteria, it was found that the mean duration of symptoms prior to operation was 10½ months. The average postoperative survival time of patients, including 3 who died immediately after operation, was 22 months. This is a minimal estimation, as it includes those still living. In 7 patients with symptoms 5 months or less, 5 survived 15 to 88 months postoperatively, and 2 deaths occurred 2 and 19 months postoperatively. Of 6 patients whose symptoms endured for a period longer than 5 months, 2 were living 11 and 12 months postoperatively and 1 died 7 months after operation, 3 died post-

Table 1

Preop. Symptoms Duration (mos.)	Postop. Survival (mos.)	Total Duration Disease (mos.)	Site	Removal
½	21½	22	fourth vent.	partial
1	17	18	parietofront.	aspirated
1	15	16	parietotemp.	partial
2	88	90	parietofront.	'complete'
5	28	33	parietofront.	'complete'
5	19*	24*	fourth vent.	partial
5	2*	7*	fourth vent.	aspirated
10	11	21	fourth vent.	partial
10	**	10**	lat. vent.	partial
13	12	25	fourth vent.	partial
13	7*	20*	fourth vent.	partial
30	**	30**	fourth vent.	biopsy
41	**	41**	fourth vent.	partial

*Dead
**Operative death

Table 2

Cellularity	Mitoses (12hpf)	Degree Differ.	Rosettes	Site	Total Survival (mos.)
4+	8	poor	P-mod.	fourth vent.	7*
3+	2	well	T-many P-many	parieto-frontal	90
3+	0	well	T-many P-many	parieto-frontal	33
3+	0	well	P-mod.	fourth vent.	24*
3+	14	mod.	P-many	fourth vent.	22
3+	1	well	T-mod. P-mod.	fourth vent.	21
3+	3	mod.	T-many P-many	fourth vent.	20*
3+	0	well	P-few	parieto-frontal	18
3+	1	mod.	T-mod. P-mod.	parieto-temp.	16
3+	14	mod.	P-rare	lat. vent.	10**
2+	0	well	T-few P-few	fourth vent.	41**
2+	0	mod.	P-mod.	fourth vent.	30**
1+	0	well	none	fourth vent.	25

T—True Rosettes
P—Pseudorosettes
*—Dead
**—Operative death

operatively. Thus, in this small group, there is an inverse relationship between duration of symptoms and survival.

Site and Removal in Relationship to Postoperative Survival (table 1). Eight of the 13 neoplasms were located in the fourth ventricle. Of these 2 occurred in patients who died postoperatively but had symptoms prior to operation for periods of 30 and 41 months; 3 died 7 to 19 months after operation with total duration of disease 7 to 24 months, and 3 were living 11, 12 and 21½ months after surgery was performed. Three tumors were found in frontal areas and all patients were living 17 to 88 months postoperatively. One patient with an ependymoma in the parietotemporal region was living 15 months after operation and has survived the disease 16 months. The tumor removed from the lateral ventricle occurred in a patient who died postoperatively but had experienced symptoms for 10 months prior to operation.

Two tumors which were considered to have been completely removed recurred at the original site, proving these observations erroneous. The tumors were located superficially in accessible regions in the parietofrontal lobes, and these patients survived the longest, 28 and 88 months postoperatively (total duration of disease 33 and 90 months). In 8 patients removal was partial, according to the notes of operation. The average postoperative survival time has been 7.2 months and total duration of the disease 22.2 months.

In one only a biopsy specimen was taken as the lesion was considered inoperable. The lesion was in the fourth ventricle and the patient died in the postoperative period after having had symptoms for 10 months. In the remaining 2 patients operations were performed with removal of the cyst wall. One of these tumors lay in the frontoparietal region and the patient was living 17 months postoperatively and has survived 18 months since the onset of symptoms. In the other case the lesion was in the fourth ventricle. The patient died 2 months after operation and survived the disease only 7 months.

Apparently tumors located in accessible and nonobstructing regions of the brain offer the longest survival period regardless of completeness of removal.

Histologic Studies

This phase was undertaken for the purpose of studying morphologic details and correlating histologic features of these neoplasms with survival rate, such as Mabon et al demonstrated in a much larger series. Due to re-operation, 4 cases provided two and three specimens at various time intervals and comparative studies could be made.

Cellularity (table 2). It is generally agreed that ependymal tumors are highly cellular neoplasms. The patient with a 4 plus cellularity died 2 months postoperatively and survived her disease for 7 months from the estimated date of onset. This was the shortest survival period of the entire series. Nine patients had neoplasms demonstrating 3 plus cellularity. Of these, 6 patients are still living, an average survival period of 29 months from onset of symptoms. This coincides closely with the value of the entire group (28.2 months). The 3 patients who died had an average survival rate of 8.3 months. Included in

this latter group is one postoperative death. Each patient had a tumor of the fourth ventricle and 2 of the 3 experienced symptoms for more than 5 months prior to operation. The 2 lesions demonstrating 2 plus cellularity occurred in patients who died postoperatively and who had experienced an estimated 40 and 30 months' duration of symptoms prior to surgery; each period was longer than the average for the entire group. Both tumors were located in the fourth ventricle. One lesion graded 1 plus was from a patient who remains alive 12 months subsequent to surgery; the total duration of the disease has been 25 months, which approaches the average of the entire group.

Although there is no relationship between the site of tumor and the degree of cellularity, a lower degree of cellularity in tumors from similar sites appears to offer a more favorable prognosis. A degree of 3 plus cellularity in lesions of the fourth ventricle indicate a much lower survival period than 3 plus lesions located elsewhere. The former show an average postoperative survival period of 10.6 months and a disease duration totaling 19.4 months; those patients having lesions not located in the fourth ventricle have average survivals of 37 postoperative months and 39.2 months of total duration of disease. These latter values are minimal since all patients are still living.

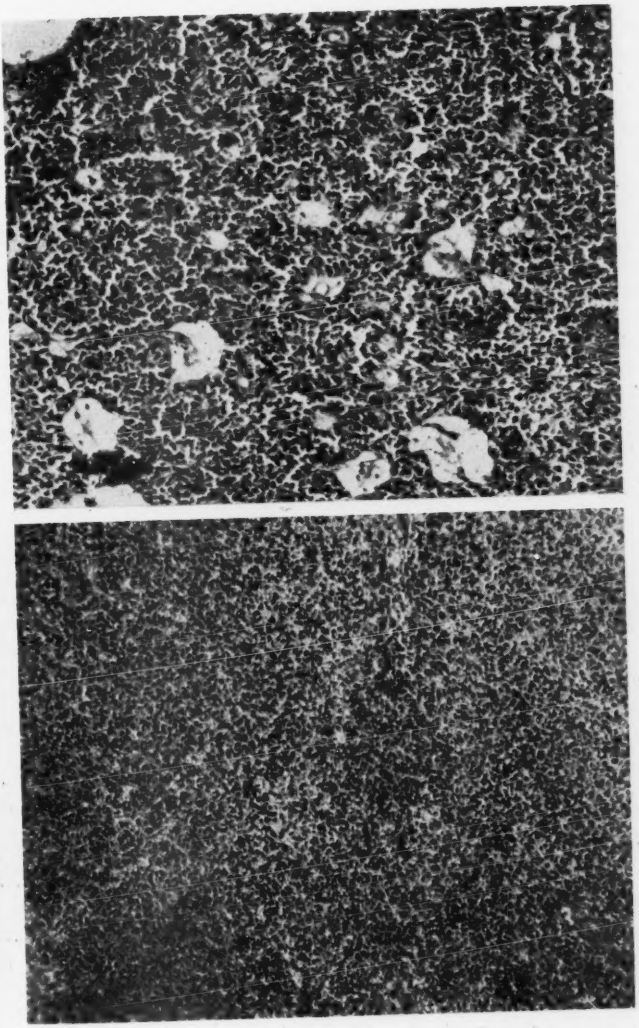
Mitoses and Pleomorphism (table 2). There appears to be a direct linear relationship between pleomorphism and the number of mitoses in these tumors. Of the 7 lesions which demonstrate mitoses 2 were considered to be uniform, 4 moderately uniform and 1 pleomorphic. Those lesions showing moderate uniformity have more mitotic figures than those considered uniform. Of the remaining lesions not showing mitoses 5 were uniform and 1 moderately uniform.

Insofar as survival is concerned there is not as direct a relationship. The average postoperative survival period in this series for the 6 patients with tumors without mitoses has been 19 months with a total duration of disease of 28 months. Conversely, the 7 lesions demonstrating mitoses occurred in patients having an average postoperative survival period of 24 months and total disease duration of 26 months.

Table 3

Case No.	Operation	Interval Between Operations (mos.)	Change in Mitoses (12hpf)	Change in Cellularity	Change in Differ.	Change in Rosettes	Change in Stroma
1	2nd	32	2−6	3+−3+	well-mod.	many-mod.	same
	3rd	43	6−12	3+−3+	mod.-mod.	mod.-mod.	more neuroglia
2	2nd	10	0−0	3+−3+	well-mod.	many-mod.	same
	3rd	17	0−0	3+−3+	mod.-mod.	mod.-few	more collagenous
3	2nd	14	1−12	3+−4+	mod.-poor	mod.-few	same
4	2nd	7	3−2	3+−3+	mod.-mod.	mod.-mod.	same

(a)



(b)

FIG. 1. (a) Tumor from initial operation revealing numerous true and false rosettes (x70). (b) Tumor from second operation 14 months later demonstrating absence of rosettes. Smaller cell type (x70).

Thus pleomorphism and mitoses in this series have been of little value in the prediction of survival.

Rosette and Pseudorosette Formation (table 2). Interestingly, there does not appear to be any direct relationship between the number of rosettes, either true or false types, and the previous histologic details noted, especially mitotic figures and cellularity. Conversely, an inverse proportion is observed, indicating that this important architectural feature is preserved in more dedifferentiated tumors.

Stroma. The stroma of ependymal tumors has received little attention. It was noted that two common types exist in these lesions: (1) a collagenous stroma not only about vessels, but also arranged as septa coursing through the tumor and among individual cells; (2) a fine fibrillary type staining blue with phosphotungstic acid hematoxylin, evident among tumor cells. One neoplasm demonstrated a third type, an amorphous matrix which stained acidophilic with hematoxylin and eosin. No relationship between the stroma, either quantitatively or qualitatively, and cellularity, mitoses, pleomorphism or survival periods could be determined.

Vessels. Ependymal tumors frequently are vascular, especially in those tumors exhibiting many pseudorosette formations with vascular cores. Reduplication of vessels was noted in only one instance. This neoplasm was also poorly differentiated, of 4 plus cellularity, and contained 8 mitoses per twelve high power fields. This patient survived 2 months postoperatively with a total disease duration of 7 months. Fibrinoid change was noted in one tumor. In this patient the disease had persisted for 20 months.

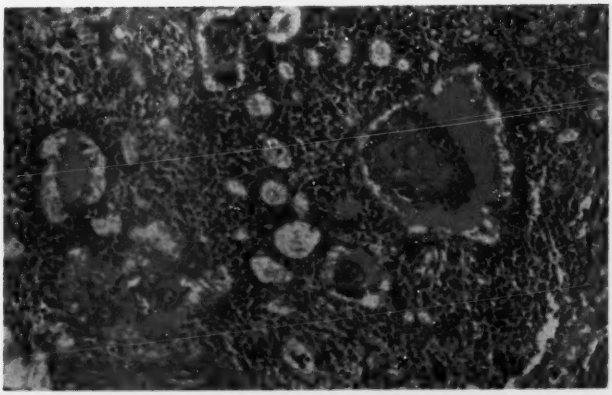
Necrosis. Areas of necrosis were noted in 5 of the 13 neoplasms studied. No relationship between this and other histologic details or survival could be formulated.

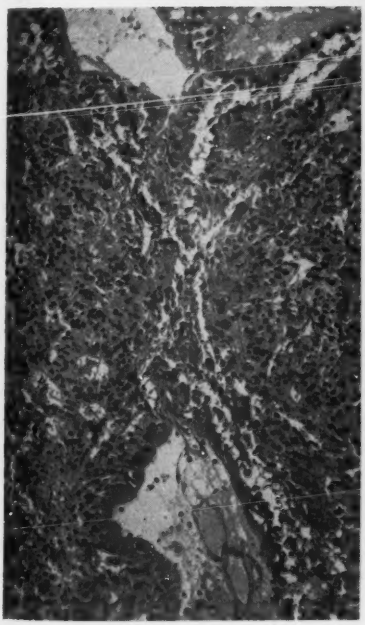
Patterns. Papillary, pseudopapillary and cystic patterns were observed. A correlation between these features and other histologic details and survival was nonexistent.

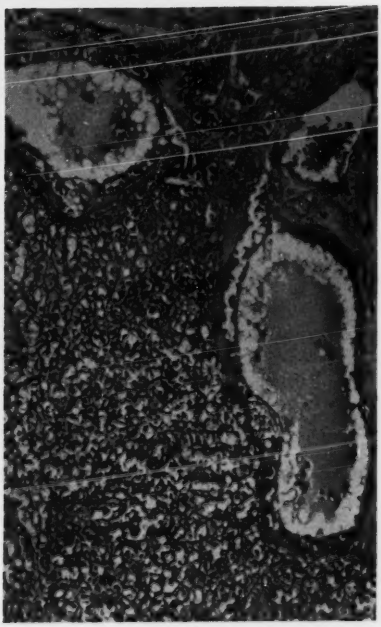
Ependymoblasts and Blepharoplasten. Although phosphotungstic acid hematoxylin stained sections were studied, no cellular inclusions structurally compatible with blepharoplasten were found. A few ependymoblasts were evident in 2 tumors. The duration of the disease prior to surgery was 41 and 30 months. Both patients died during the immediate postoperative period.

Roentgen Therapy. This type of therapy was employed in 4 cases following surgery. The dosage ranged between 3,000 and 5,000 r. Two patients received second courses of irradiation. Three of the group are alive 12, 21½ and 17 months postoperatively. One patient died 19 months after operation. This patient's tumor was in the fourth ventricle and histologically demonstrated uniformity with 3 plus cellularity and no mitoses per twelve high power fields. Of the 3 surviving patients 2 also had tumors in the fourth ventricle. One was of moderate cellularity and demonstrated 14 mitoses per twelve high power fields; two courses of irradiation were given in this instance and the patient is alive 22 months after surgery. The other patient with a lesion of the fourth ventricle has survived 12 months postoperatively. This tumor was judged to

(a)







(b) (c)

FIG. 2. Interval studies. (a) Tumor from initial operation. Frequent rosettes (x70). (b) Tumor from second operation 10 months later showing reduction in number of rosettes (x70). (c) Tumor from third operation 17 months subsequently; rare rosettes, small cysts, dense collagenous stroma.

be uniform; it had no mitoses, and demonstrated a 1 plus cellularity. The remaining patient who is living 17 months after operation had an ependymoma in the parietofrontal region. This tumor was uniform with 2 plus cellularity and was free of mitotic figures. The group is too small to permit conclusive evaluation; however, the satisfactory response obtained in that lesion with 14 mitoses per twelve high power fields warrants further investigation of the effect of irradiation upon ependymal tumors. Since irradiation was not used in any cases presenting interval specimens, its effect upon the histology of these tumors could not be determined.

Interval Studies (table 3). Neoplasms of 4 patients could be studied at time intervals since they were submitted to two or more operative procedures. In 3 of these instances the tumor was located in accessible and relatively nonobstructing areas of the brain such as the parietofrontal region. It is apparent in table 3 that, in general, there is an increase in mitoses, and decrease in uniformity and number of true rosettes and pseudorosettes (figs. 1 and 2). There was no apparent relationship to the time interval between operations and degree of change. Neither is change consistent among the features of rosettes, pseudorosettes, mitoses and other histologic elements.

Comment

Ependymoma is a rare type of glioma comprising approximately 3.7 per cent of all brain tumors.[7] These cases represent 2.7 per cent of all gliomas seen at the Cleveland Clinic during the period 1933 to 1948. Furthermore, the sparsity must necessarily emphasize the importance of the individual tumor. This is as significant in the study of biologic phenomena as are larger statistical evaluations. The study of only one small area of tumor may be justifiably criticized; yet, its importance is obvious to the pathologist who may be called upon to offer prognosis as to survival in a case in which only a small portion of tumor is available for study. The presence of mitotic figures in over one-half of all cases in this series is at variance with the concept that ependymomas contain no mitoses.

Although the work of Mabon, Svien, Kernohan and Craig[4] has offered much in the correlation of histologic features with prognosis, it has been observed in this investigation that the actual grading of these neoplasms is, as in many malignant tumors, exceedingly difficult, especially when correlating classification with survival. This study indicates that the clinical features associated with site of tumor, and the duration of symptoms prior to operation, are of greater importance insofar as survival is concerned than any single histologic feature or group of features. The findings corroborate Bailey's and Cushing's original contention that these tumors are malignant due to site.

Conclusions

1. Thirteen ependymomas were studied from a clinical as well as pathologic standpoint.

2. The grading of these tumors is difficult due to inconsistency among the histologic criteria used in determining the degree of differentiation.

3. The site of tumor, ease of surgical removal, and preoperative duration of symptoms appear to influence survival more than any single histologic feature or group of features.

References

1. Bailey, P.: Tumors arising from ependymal cells. Arch. Neurol. and Psychiat. **11**:1 (Jan.) 1924.
2. Bailey, P. and Cushing, H.: A Classification of the Tumors of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis. Philadelphia, J. B. Lippincott Company, 1926.
3. Bailey, cited by Davidoff, L.: Brain tumors; their pathology, symptomatology, diagnosis, and prognosis. Reprinted from Psychiat. Quart. Vols. 4 and 5, April 1930 to April 1931.
4. Mabon, R. F., Svien, H. J., Kernohan, J. and Craig, W. M.: Ependymomas. Proc. Staff Meet. Mayo Clin. **24**:65 (Feb. 2) 1949.
5. Penfield, W.: Principles of pathology of neurosurgery. Chapter 6, Reprint No. 15, p. 303, 1932.
6. Kernohan, J. and Fletcher-Kernohan, E.: Ependymomas. A. Research Nerv. and Ment. Dis. Proc. **16**:182, 1937.
7. Scheinker, I. M.: Neurosurgical Pathology. Springfield, Charles C Thomas, 1948.

SKELETAL IDENTIFICATION*

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THE problem of skeletal identification is older than anatomy, anthropology, or medicine. Man's early use of bone marrow for food, his utilization of bones for weapons, and his attempts at surgery offer indirect evidence that his knowledge of the skeletal parts was considerable. In our own American Indian cultures, bone played an important role. Jaw bones of deer were used as scrapers; their vestigial ulnae as well as the long bones of birds were fashioned unto points used for piercing. The preservation of skulls of slain enemies by many primitive people gave the leaders opportunities which they probably did not utilize for contemplation and observation of individual skeletal differences; but certainly they recognized differences between human skulls and others.

FIG. 1. (a) Dorsal view of bear paws. The terminal phalanges have been removed in skinning. These paws were sent to the coroner's office in the belief that they were human feet.

Address delivered at the annual convention of the Ohio State Coroners' Association, May 23, 1951.

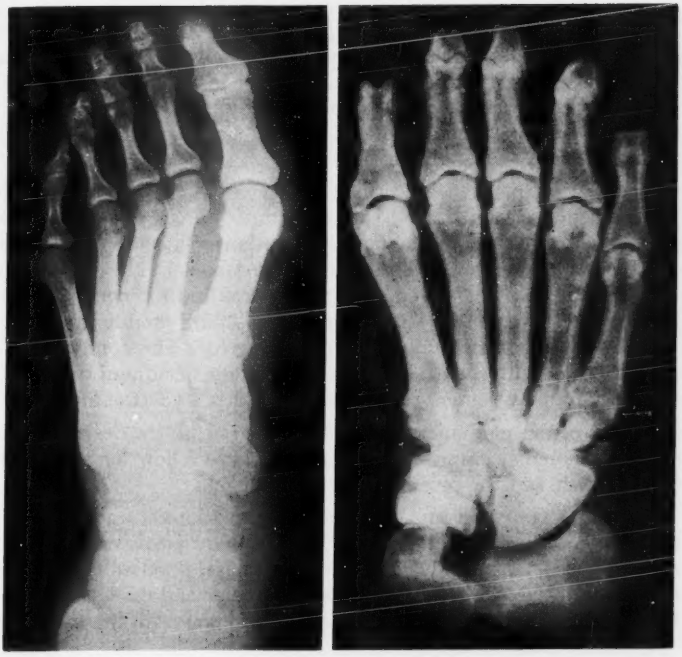


FIG. 1. (b) Radiograph of human foot, left, and bear paw right, both of the left foot (human dorsal view, bear plantar view).

Today the medical profession is called upon frequently to determine the nature of skeletal finds. Frequently animal bones are mistaken for human bones. Dutra,[1] for example, in his excellent article on skeletal identification, points out the close resemblance between a human femur and that of a bear. Recently a pair of bear's paws (fig. 1), found on a Cleveland city dump, were sent to Dr. S. R. Gerber, Cuyahoga County Coroner, for identification in the belief that they were human remains. If the finds prove to be of human origin, further questions as to age, sex, race, stature, and individual peculiarities immediately arise. In the event of murder or violent death suspected in connection with skeletons unearthed by chance from shallow graves, from skeletal fragments found in the ashes of buildings destroyed by fire or explosion, or washed up on beaches, their identification becomes a matter of public concern.

To qualify as an expert on skeletal identification demands a long apprenticeship which the medical practitioner and the coroner are unable to serve unless their primary interests follow these channels. There are a number of criteria developed over the years, chiefly by anatomists and anthropologists, that enable anyone reasonably acquainted with the human framework or its isolated parts or fragments to determine with some degree of accuracy the sex, race, age and stature of the unknown skeleton.

Age

Perhaps the first question in the mind of the examiner of skeletal remains concerns the age of the skeleton. If skull and/or long bones are present, this question may be answered with considerable accuracy. Tooth eruption, epiphyseal union of long bones, fontanel closure and occipital suture closure are the best criteria to determine skeletal age.

The fontanels of the skull are usually six in number. An anterior fontanel lies at the junction of sagittal and coronal sutures, an occipital or posterior at the junction of sagittal and lambdoid sutures, a lateral at the sphenoid-parietal junction, and a posterior lateral or mastoid fontanel at the masto-occipital junction. The last two are paired. The two lateral and the occipital fontanels are closed shortly after birth, usually within the first 2 months; the frontal or anterior closes about the middle of the second year. The condition of these fontanels, together with the extent of eruption of the deciduous dentition, permits fairly accurate assessment of age within the first 2 years of life.

The status of the permanent dentition together with the degree of fusion of the occipital elements comprise the safest criteria to follow for age evaluation between the fifth and the seventeeth year (table 1).

The occipital bone consists of a squamous, two lateral and a basilar part and the difference in time of its various suture fusions yields valuable information regarding skeletal age. The squamous and lateral parts unite at from 4 to 5 years. Between the sixth and seventh year the basilar and the lateral parts join. The basilar part does not fuse with the sphenoid bone until the twenty-second to twenty-fifth years.

Thus if the squama and lateral parts of the occipital are united, and the first permanent molars are beginning to erupt in a skull under examination, the skeleton would be between 5 and 6 years old.

The interval between 17 and 25 can be determined rather accurately by noting the relationship between the eruption of the third permanent molars and the degree of fusion between basioccipital and sphenoid bones. If the third molar has erupted and the occipitosphenoid suture is open, the skull is over 17 and undoubtedly under 22. If, with the eruption of the third molar, the occipitosphenoid union is almost completed the age is probably near 25 years.

Beginning about the fifteenth year, epiphyseal union of the long bones proceeds in somewhat orderly fashion. Table 2, based on the study of Stevenson,[6] is a reliable guide for assessment of age between 15 and 30 years.

Time of cranial suture closure, aside from the occipital sutures already mentioned, is another approach to the problem of age assessment. Todd and Lyons,[7] on the basis of many observations, have set up a tabulation which is of some value in age assessment (table 3). Perhaps the greatest single fact that emerges from their work is the evidence of delay of initiation of mastoid and temporal and sphenoid closures in comparison with sagittal and coronal fusions. Associated with this finding is a further fact of practical value: the mastoid, temporal and sphenoid sutures are not completed until late in life,

Table 1

TABLE OF TOOTH ERUPTION (After Gray)

Milk dentition	
Lower central incisors	6 to 9 months
Upper incisors	8 to 10 months
Lower lateral incisors and first molars	15 to 21 months
Canines	16 to 20 months
Second molars	20 to 24 months
Permanent dentition	
First molars	6th year
Two central incisors	7th year
Two lateral incisors	8th year
First premolars	9th year
Second premolars	10th year
Canines	11th to 12th year
Second molars	12th to 13th year
Third molars	17th to 25th year

Table 2

AGE ORDER OF EPIPHYSEAL UNION IN MAN

Order	Begins (Year)	Completed (Year)
1. Distal extremity of humerus	15 (?)	Before 17
a. Medial epicondyle	16 (?)	Before 17
2. Coracoid process of scapula	15	Before 16
3. Three elements of innominate	15 (?)	Before 17
4. Head of radius	Beginning of 18	End of 18
a. Olecranon of ulna	16 (?)	17
5. Head of femur	Beginning of 18	18
a. Lesser and greater trochanter	Lesser slightly earlier, greater same as head	18
6. Tuberosities of ribs	18 (very unreliable)	22
7. Distal extremities of tibia and fibula	18	End of 18
8. Proximal extremity of tibia	Beginning 18	Beginning 20
a. Proximal extremity of fibula	Beginning 18	Beginning 20
9. Distal extremity of femur	Beginning 19	Beginning 20 (or earlier)
10. Tuberosity of ischium	Beginning 18	Beginning 19
11. Distal extremities of radius and ulna	Beginning 19	19
12. Head of humerus	19	20
13. Crest of ilium	19	21
14. Heads of ribs	20 (very unreliable)	22
15. Ramal epiphysis of pelvis	19	22
16. Clavicle	22 (?)	28

Table 3

CRANIAL SUTURE CLOSURE (From Todd and Lyons)

Suture	Begins (Year)	Termination or Peak (Year)
Sagittal		
pars obelica	20	29 to 3.9*
pars lambdica	21	29 to 2.4
pars verticis	21	29 to 2.7
pars bregmatica	26	29 to 2.9
Coronal		
pars bregmatica	26	29
pars complicata	26	29
pars pterica	22	50 to 3.8
Lambdoid		
pars lambdica	21 to 26	30 to 2.3
pars media	21 to 26	30 to 1.9
pars asterica	26	30 to 0.6
Masto-occipital		
pars superior	28	old age
pars media	28	old age to 3.5
pars inferior	26	62 to 3.6
sphenotemporal	36 to 37	65
squamous	38	65
Parietomastoid	39	64
Sphenoparietal	28	
Sphenofrontal		
pars temporalis	28	65 to 4.0
pars orbitalis	28	46 to 3.8

*Todd and Lyons set up a scale ranging from 1 to 4 to denote the degree of fusion. Thus 1 indicates the initiation and 4 the completion of fusion.

Table 4

PELVIC DIMENSIONS*

False Pelvis	Male (mm)	Female (mm)
Greatest distance between crests of ilia (externally)	287	279
Distance between anterior superior spines of ilia	241	233
Distance between front of symphysis pubis and first sacral spine	183	178

True Pelvis	Male Inlet	Male Cavity	Male Outlet	Female Inlet	Female Cavity	Female Outlet
Transverse diameter	127	119	89	132	127	119
Oblique diameter	119	114	102	127	132	89
Anteroposterior diameter	102	107	79	114	127	114

*Modified from Quain, ed. 10.

while sagittal, coronal and lambdoid are, with one exception (pars pterica), virtually completed by 30 years of age.

If all sutures save those associated with the mastoid bone are well on the way to fusion in a given skull, it is most likely under 30 years old. If the squamous portion of the temporoparietal suture is partly fused, the skull is likely between 45 to 55 years old. If that suture is obliterated, the skull is probably over 65.

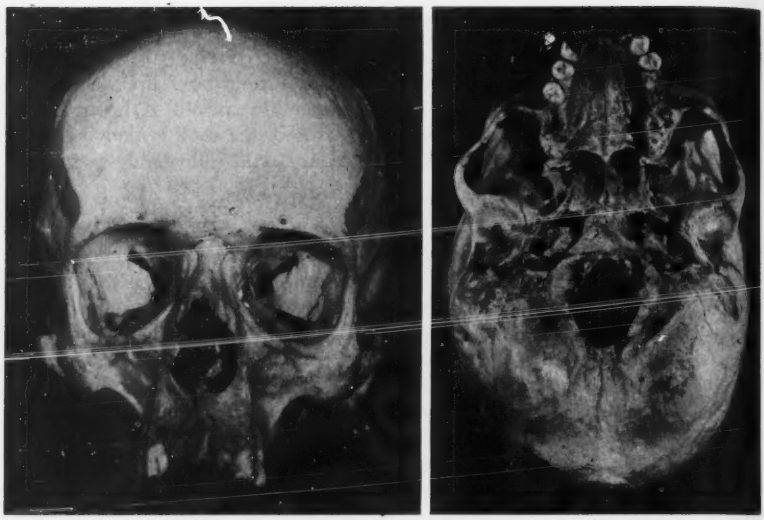
Sex

Certain sexual skeletal characteristics facilitate the determination of the sex if the skeleton is of normal pattern or if it is complete. If one deals with fragments or with an atypical skeleton, e.g., the skeleton of a large muscular female of robust type, identification becomes more difficult.

The pubic angle is over 70 degrees and rounded in the female, and less than 70 degrees and more angular in the male. This is probably the best single criterion. Table 4 shows other sexual differences both in the true and in the false pelvis. If the pelvis is fractured, the sex may easily be confused. For example, in the great Ohio gas explosion three of us identified a charred torso, minus head, legs, and arms as that of a male on the basis of the x-ray plates of the fractured pelvis. Dissection of the few remaining fragments of charred internal organs indicated the remains to be those of a female.

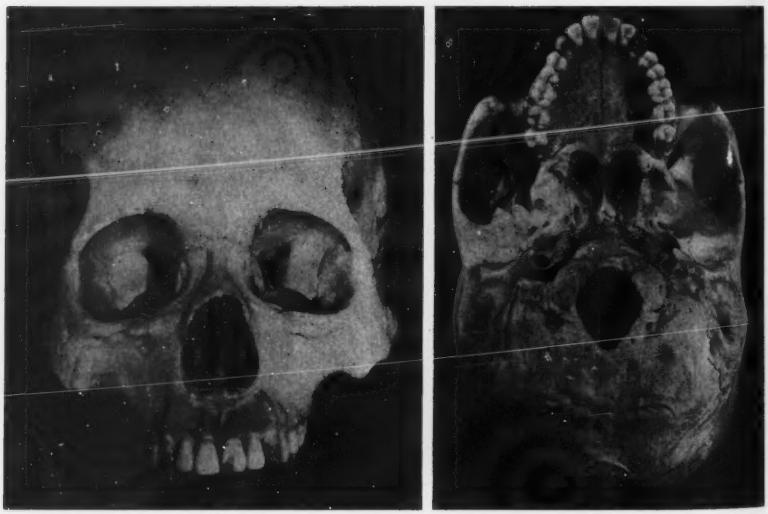
(a) (b)

FIG. 2. Negro Skull. (a) Note particularly wide nasal aperture with dull lower margin, deep canine fossae, large orbits, long fused nasal suture, relatively narrow forehead, flat temporal region. (b) Compare long hard palate and narrow dental arch with that of the Mongoloid (fig. 4)



(a) (b)

FIG. 3. White Skull. (a) Observe sharp lower margin of nasal aperture, deep canine fossae, relatively small orbits, tendency toward streamlining of malar bones. (b) Narrow hard palate and narrow dental arch resembling that of the Negro.



(a) (b)

FIG. 4. Mongoloid Skull (North Korean). (a) Shows angularity and prominence of malar bones, absence of pronounced canine fossae, angularity of orbits, wide nasal aperture with tendency toward dull lower margin resembling that of the Negro. Shovel-shaped incisors. (b) Short wide hard palate and accentuated arching of dental arcade.

In general female bones are more delicate, the bony markings for muscular attachments less pronounced than those of the male. The articular heads also are relatively smaller. The pelvic outlet in the female is less constricted than in the male. The lower part of the sacrum is bent backward. It is shorter and broader, while the greater sciatic notch is wider and more shallow than in the male. The margins of the pubic bones are inclined outward in the female and the iliac margins do not flare as greatly as in the male.

The cranium is smaller, less rugged, more delicate than in the male. All markings for muscle attachments (temporal lines, nuchal lines, mastoid processes, styloid processes) are less pronounced in the female than in the male. The forehead is more bulbous, the eyebrow ridges are less pronounced, the malar bones are less rugged, the hard palate and the teeth are smaller, and the lower jaw is smaller and has a lesser chin projection than in the male.

Race

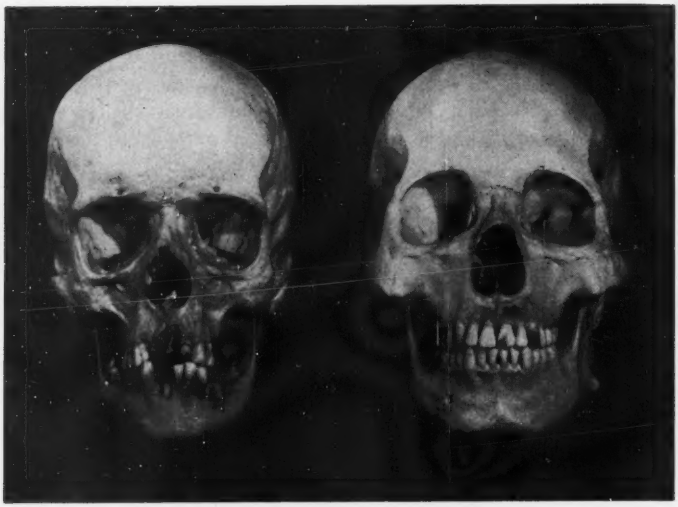
It is of great importance in the evaluation of skeletal data to know the race of the skeleton. In connection with this problem one difficulty results from the fact that we are frequently confronted with racial mixtures of varying degree. Each of the major races, i. e., the White, Negro, and Mongoloid is marked skeletally by certain well-defined features that become greatly moderated in instances of racial admixtures.

Outstanding Cranial and Postcranial Features of the Negro Skeleton

(Figs. 2, 6, 7)

Cranial

Wide nasal aperture, dull lower margin.
Rudimentary nasal spine.
Deep canine fossa.
Prognathism frequently pronounced.
Close dense texture of relatively fresh skull.
Chin may be poorly developed.
Jaws may bulge subnasally.
Broad nasal bridge.
Long nasal suture often fused in adult skull.
Palate and dental arches long and narrow.
Teeth exceed those of a white skeleton in size.
Impacted third molars rare.
Orbit low but not tilted down or out.
Glabella not protrusive.
Forehead symmetrically rounded side to side and from front to back, inclines to narrowness.
Female forehead often bulbous.
Temporal region flat.



(a) (b)

FIG. 5. (a) White skull. (b) Mongoloid with complete dentition.

(a) (b)

FIG. 6. (a) White skull. (b) Negro skull.

Crania generally long headed.
Cranial constriction just behind coronal suture.
Occipit protuberant.
Attachments for neck muscles and ligaments ordinarily not strongly marked.
Cranial sutures less serrated than in whites.
Molars sloping as in whites.
Canine fossa pronounced.
Malar bone streamlined.

Postcranial

Bones slender, articular heads small.
Pelvis narrow and high.
Bones of forearm and leg long relative to upper segments of respective limbs.

The greatest single characterizing feature is probably the dull lower margin of the nasal aperture which stands in great contrast to the sharp-edged margin in the white skull—the nasal spine too is well defined in the white skull and relatively shorter in the Negro.

Outstanding Cranial and Postcranial Features of the White Skeleton

(Figs. 3, 5, 6, 7)

Cranial

Small jaws, pinched palates.
High narrow nasal bones.
Lower and upper nasal border sharp.
Prominent nasal spine.
Chin eminence more pronounced than in non-whites.
Depression of nasofrontal suture.
Brow ridges prominent in male, more developed laterally.
Receding forehead more common in male whites than in Negro.
Tortuous cranial sutures.
Mastoid and styloid processes larger than in Negro.
External occipital protuberance, conical or hooked.
Straight orthognathous face, devoid of prognathism.
Deep canine fossa.
Malar bone moderately streamlined.

Postcranial

Bones thicker, more massive than Negro.
Joints larger than Negro.
Pelves wider and more rugged than in Negro skeleton.
Muscular skull markings prominent.

Outstanding Cranial and Postcranial Features of the Mongoloid Skeleton

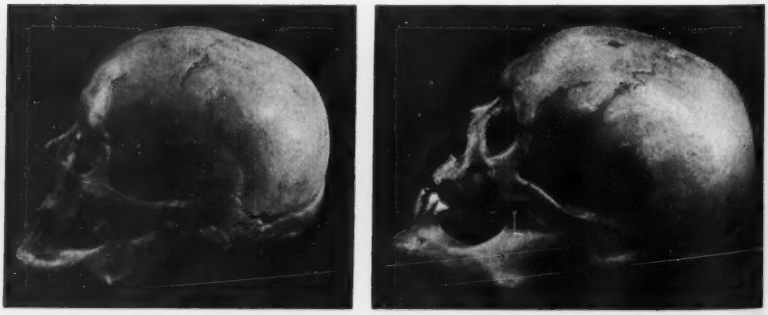
(Fig. 4, 5, 8)

Mongoloid skeletal features vary greatly within the race.

The features are more rugged and primitive in appearance in Eskimo and certain Siberian tribes than in Japanese, Korean, Chinese and certain Amerindian skeletons. The following characteristics appear quite general:

Cranial

Outstanding feature is the angularity and prominence of malar bone.
Body of malar deeper and more massive than in non-Mongoloid, produces flat appearance of Mongol skull.
Canine fossa disappears.
Slight or no nasofrontal suture depression.
Root or nose broad and flat.
Middle pillar (nasal) wide.
Top of nasal bones narrow, flare out distally.
Below nasion nasal root is depressed.
Borders of nasal aperture dull, spine small.
Some alveolar prognathism.
Palate and dental arcades short and wide.
Shovel-shaped incisors.
Glenoid fossa more shallow than in Negro or white.
Brow ridges not prominent.
Forehead moderately high.
Ridge pole like elevation of sagittal suture.
Skull sutures simple.
Temporal region not building.



(a) (b)

FIG. 7. (a) Lateral view of white skull with somewhat bulging temporal bone. (b) Negro skull with flattened temporal bone. The canine fossa is deep in both races.

FIG. 8. Base of Mongoloid skull. Note open temporal-occipital sutures which close normally between 55 and 62; open basioccipital-sphenoid suture that closes normally at 25; short wide palate and horseshoe shaped dental arch, and pronounced angularity of malar bones.

Postcranial

Articulations are smaller, long bones more slender than whites except in primitive Eskimo types.

The question of the value of determining long-headedness or round-headedness is frequently raised. The Negro, the Mongoloid, the Mediterranean and Nordic white generally run to long-headedness; the Alpine European is more commonly round-headed. The Armenianoid types have peaked heads as do the Dinaric from Southeastern Europe.

The American types commonly represent mixtures. The ancient pure Negro types also are tempered by interbreeding. Anglo-Saxon, Mediterranean and Alpine mixtures produce skeletal results difficult to translate in many skulls. Table 5 (from Dutra) shows the differences in the measurements of skulls of various races.

The studies of Karl Pearson[4] which led to a series of formulas for determination of stature from dried bones deserves prominent mention in any study directed to skeletal identification (table 6). He was the first to develop (1899) reliable formulas for such determinations from individual bones or from com-

Table 5

RACIAL DIFFERENCES IN SKULLS

Character	North European	Caucasoid Central European	South European	Mongoloid	Negroid
Skull length (center of forehead to occiput)					
Male	183-192*	Below 175	183-192	Below 175	183-192
Female	175-184	Below 167	175-184	Below 167	175-184
Skull breadth (maximum breadth between parietal bones)					
Male	132-142	Above 151	132-142	Above 151	132-142
Female	126-136	Above 145	126-136	Above 145	126-136
Skull height (anterior margin of foramen magnum to junction of sagittal and coronal sutures)					
Male	Above 138	Above 138	Approx. 138	128-138	Below 128
Female	Above 131	Above 131	Approx. 131	121-131	Below 121
Face height (upper) (tip of upper jaw, excluding teeth, to suture between nasal and frontal bones)					
Male	75-80	75-80	Approx. 75	75-80	Below 69
Female	70-75	70-75	Approx. 70	70-75	Below 64
Face breadth (maximum breadth between cheek bones)					
Male	Below 128	136-144	Below 128	Above 144	Below 128
Female	Below 118	126-134	Below 118	Above 134	Below 118
Cranial index $\frac{\text{Breadth of skull}}{\text{Length of skull}} \times 100$	Below 75	Above 80	Below 75	Above 80	Below 75
Index of height $\frac{\text{Height of skull}}{\text{Length of skull}} \times 100$	Above 75	Above 75	Approx. 75	70-75	Below 70
Nasal index $\frac{\text{Nasal breadth}}{\text{Nasal height}} \times 100$	Below 47	51-53	Below 47	Below 47	Above 51

*All measurements are expressed in millimeters.

binations of bones although Manouvrier (1892) and Rollet (1889), earlier, had laid the foundations for such studies. I have found the formulas highly accurate when applied to material available to me. Ordinarily variations between the theoretical values and the actually established values are less than 2.5 cm.

The lengths are measured in centimeters. In the case of the femur the maximum length from head to distal end is taken. If the oblique length is used, add 0.32 to the femur length if from a male or 0.33 from a female, before applying the equation. In measuring the length of the tibia, the length to the distal articulating surface is taken, and not to the tip of the styloid process. The values in centimeters (found by direct measurement of the bones in question) are multiplied by the adjacent constants and the result added to the first constant in the formula; this gives stature in centimeters. The formulas have been determined from right members. According to Pearson[4] a slight error of the second order may arise when the left member is used. Use of formulas e, f, and i show the lowest factor of error.

With the indicated tools whose value has been determined by long experience, one should not err too greatly in skeletal identification. But with all these criteria—suture closing, racial characteristics, formulas for determining stature—it is still an easy matter to make wrong evaluations. I have, for example, in my collection a white skull presumably about 25 years of age, if the status of the cranial sutures were authentic. This skull is edentulous, the frontal, parietal,

Table 6

STATURE RECONSTRUCTION FORMULAS

Male Stature

a. S=81.306+1.880 femur
b. S=70.641+2.894 humerus
c. S=78.664+2.376 tibia
d. S=85.925+3.271 radius
e. S=71.272+1.159 (femur+tibia)
f. S=71.443+1.220 femur+1.080 tibia
g. S=66.855+1.730 (humerus+radius)
h. S=69.788+2.769 humerus+0.195 radius
i. S=68.397+1.030 femur+1.557 humerus
k. S=67.049+0.913 femur+0.600 tibia+1.225 humerus−0.187 radius

Female Stature

a. S=72.884+1.945 femur
b. S=71.475+2.754 humerus
c. S=74.774+2.352 tibia
d. S=81.224+3.343 radius
e. S=69.154+1.126 (femur+tibia)
f. S=69.561+1.117 femur+1.125 tibia
g. S=70.542+2.582 humerus+0.281 radius
h. S=67.435+1.339 femur+1.027 humerus
i. S=67.469+0.782 femur+1.120 tibia+1.059 humerus−0.711 radius

*All measurements are expressed in millimeters.

occipitoparietal sutures are open. Everything indicates that the skull is about 20 to 25 years old, save that the individual was approximately 56 years old at the time of death.

Generally stature, body types and race may be determined with considerable accuracy. This knowledge supplements, in criminal or anthropologic investigation, the findings and speculations obtained from other avenues of approach.

References

1. Dutra, F. R.: Identification of person and determination of cause of death from skeletal remains. Arch. Path. **38**:339, 1944.
2. Hooton, E. A.: Up from the Ape. New York, The Macmillan Company, 1946.
3. Manouvrier, M.: Memoires de la Societe d'Anthropologie de Paris. **4**:384, 1892.
4. Pearson, K.: Philosophical Transactions of the Royal Society. **192**:169, 1899.
5. Rollet, E.: De la Mensuration des Os Longs des Membres—Lyons, 1889.
6. Stevenson, P. H.: Age order of epiphyseal union in man. Am. J. Phys. Anthropol. 7:53, 1924.
7. Todd, W. T. and Lyons, D. W.: Ectocranial closure in adult males of white stock. Am. J. Phys. Anthropol. **8**:23-46, 47-71, 149, 168, and **7**:325-384, 1925.

DILATATION AND CURETTAGE

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DILATATION and curettage, though one of the commonest of gynecologic operative procedures, is not done frequent enough and often is performed in a manner which makes its value dubious. Like so many other so-called minor procedures, it has suffered from being thus classified and has been utilized by the casual surgeon, with subsequent grave sequelae.

This procedure may be diagnostic or therapeutic and, on occasion, a combination of the two. It is in the diagnostic field that the greatest number of errors occur. When the procedure is properly carried out, tissue from the endocervix may be obtained separately from that in the uterine cavity (fractional curettage), thus making it possible to differentiate cervical from corpus abnormalities. The curet also permits a modified digital exploration of the uterine cavity which demonstrates irregularities. By careful gross examination of the tissue removed, it is often possible to obtain a clue as to the presence or absence of malignancy. Tissue removed should always be subjected to careful microscopic examination. Careful bimanual and rectovaginal examination should, of course, always be combined with dilatation and curettage. When a patient is under anesthesia, we are presented with an excellent opportunity for complete and thorough examination without the apprehension and fear of pain imposed by consciousness. Significant ovarian disease may also be found.

Indication

The commonest indication for diagnostic dilatation and curettage is bleeding. In the younger age group, so-called functional bleeding is the most frequent cause. Such a diagnosis, however, is not possible without a confirmatory dilatation and curettage. A curettage is preferable to endometrial biopsy performed in the office since, with the patient anesthetized, it is possible to empty thoroughly the uterine cavity, providing a secondary therapeutic effect. Thorough curettage will eliminate, in most cases, the endometrial polyp as the cause of bleeding irregularities. Oftentimes repeating the procedure in this group will control hemorrhage and avoid more drastic procedures, thereby maintaining the childbearing function.

When one is seeking the cause of intermenstrual bleeding in the presence of a clean cervix, fractional curettage should be carried out and the tissues from the two sites examined separately. It is also wise, in these instances, to carry out a diagnostic conization as well. Any woman experiencing intermenstrual spotting or bleeding, with no obvious cervical source, should have the benefit of such an examination.

In the menopausal age group, aberrations from normal are not unusual. The physician investigating the problem must eliminate carcinoma as a cause.

At the time of menopause, bleeding should be less frequent, of shorter duration and of diminished quantity. Due to the present day tendency to misuse hormonal therapy, irregular or profuse bleeding during the menopause is increasingly common. When this problem presents itself, the only method of proving that hormones have caused the bleeding is by thorough endometrial curettage. It is always possible for a patient to develop carcinoma concomitant with hormonal therapy. Menopausal irregularities often can be controlled by dilatation and curettage, thereby eliminating such radical methods as castration or hysterectomy. Unexplained discharge is also a frequent symptom of carcinoma of the endometrium and, in such cases, dilatation and curettage is a mandatory procedure.

Any woman who experiences postmenopausal bleeding or spotting, with or without hormonal therapy, should have dilatation and curettage with thorough examination under anesthesia in order to exclude carcinoma and ovarian disease. One may complete the dilatation and curettage without having discovered the origin of the bleeding, but malignancy, for the most part, will have been eliminated as a causative factor.

The surgeon is constantly confronted with the problem of whether or not dilatation and curettage should be performed for the asymptomatic cervical polyp. As a general rule a Papanicolaou smear should be taken, followed by removal of the polyp in the office (preferably with a tonsil snare). Should the polyp recur, a dilatation and curettage is indicated. Conversely, a polyp which is associated with abnormal bleeding should be removed under anesthesia and accompanied by a thorough curettage.

An increasingly common indication for dilatation and curettage is a positive Papanicolaou smear. When this occurs, without evidence of cervical abnormality, a fractional curettage should be performed with incidental conization. A more radical procedure such as hysterectomy is never justified on the evidence of a single positive smear, and every attempt should be made to find the source of the atypical cells.

Another diagnostic possibility, unfortunately often overlooked, is that of combining dilatation and curettage with abdominal pelvic exploration. This is particularly important when there is any associated irregular vaginal bleeding. If dilatation and curettage are performed prior to laparotomy, a final pelvic evaluation may be made before performing an abdominal exploration. In the process the cervix is observed and abnormalities are treated intelligently. Practically every practicing gynecologist has seen patients upon whom subtotal hysterectomies were performed for bleeding which later proved to have been cervical in origin. Hendricks[1] has recently reported 6 cases of this type.

When the indication for hysterectomy is a myomatous uterus, with symptoms of bleeding, it does not always mean that bleeding is due to the myoma; neither does it preclude the presence of associated carcinoma of the endometrium. When a diagnosis of carcinoma is thus made, or when suspicion regarding its presence exists, further operative procedure should be suspended.

Primary hysterectomy is not the treatment of choice in corpus carcinoma. Instead, preliminary irradiation followed in 6 weeks by total hysterectomy and bilateral salpingo-oophorectomy is generally accepted as more satisfactory therapy. Pelvic examination at best is inexact and only through constant determined effort can skill be attained. There is no better way to test the accuracy of palpation than by examination immediately followed by laparotomy.

In dealing with the problems of infertility, it is possible to establish the presence or absence of ovulation in the current cycle—providing proper timing is observed. Dilatation and curettage should be carried out on the first day of the menstrual period in these cases. It is preferable to endometrial biopsy in many instances since it provides more complete information.

Dilatation and curettage has been suggested for the evaluation and treatment of dysmenorrhea. In carefully selected cases this is a valuable procedure and one which should be initiated as a therapeutic measure before attempting intra-abdominal intervention. It is particularly of value in those cases of primary dysmenorrhea which are refractory to medical therapy.

Dilatation and curettage is a generally accepted therapeutic measure in treating retained products of conception and pregnancy complications such as moles.

Method

Much of the reluctance to perform a dilatation and curettage is due to shortage of hospital beds. Many patients object to the necessary time loss and the expense involved in hospitalization. These objections can be overcome by performing the examination as an in-and-out procedure, without danger of increased morbidity and without unusual complications. Patients at the Cleveland Clinic Hospital are operated upon under pentothal and gas-oxygen anesthesia, and discharged when fully recovered. The operation can be performed on Friday or Saturday and the patient is able to return to work the following Monday morning. If complications arise during the procedure or if carcinoma is suspected, she may be admitted for observation. Perineal shaving is omitted prior to dilatation and curettage and usually only a thorough perineal and vaginal preparation with aqueous zepharin or merthiolate is used. By this procedure discomfort is reduced considerably.

Our method consists of a preliminary examination under anesthesia, followed by sounding of the cervix to confirm the uterine position and depth of the cavity. The cervix is then carefully dilated with a Wylie dilator and the largest curet which the cervix will admit is employed. The cavity is scraped systematically, inserting the curet the full depth of the uterus, holding it against the wall and completely withdrawing it. This maneuver is repeated in similar manner until the whole cavity has been thoroughly covered. Scrubbing motions should be avoided, since this tends to fragment the endometrial tissue and make satisfactory diagnosis more difficult. A sponge is placed in the vagina posterior to the cervix to collect the specimen which is immediately transferred to a specimen bottle and covered with fixative.

The larger the curet employed the more complete will be the coverage of the cavity while the danger of perforation will be decreased. When the cervix is adequately dilated caution must be observed in covering the entire cavity of the uterus as an unusually small carcinoma may easily escape detection. Polyps, too, may be overlooked.

Contraindications and Complications

The presence of acute cervical lesions or vaginitis are contraindications, since pelvic inflammatory disease may be a sequela. The chronically infected cervix can be treated by means of preliminary conization, thereby eliminating the infection and decreasing the chance for infectious material to enter the uterine cavity. A preliminary conization also makes dilatation of the cervix easier. There have been objections to dilatation and curettage associated with cervical procedures, but Crossen[2] has demonstrated the value of the procedure by discovering 8 cases of carcinoma of the endometrium at the time of conization.

Lacerations of the cervix may occur when forceful dilatation is employed. Perforation of the uterus is not an infrequent complication despite precaution and awareness of its possibility. Predisposing factors are inadequate preliminary cervical dilatation, too small or too large a curet, a large, boggy uterus (as evidenced in instances of incomplete abortion), or a uterus with soft spots (such as one containing an area of carcinoma). The curet should be held like a pencil, to minimize further the chances of perforation.

When perforation occurs, one should suspend further attempts at curettage and return the patient to bed. If there is evidence of excessive bleeding into the peritoneal cavity, laparotomy should be performed to repair the hole in the uterus. Evidence of infection should be treated with appropriate antibiotic measures although prophylactic chemotherapy may occasionally be employed. A further complication of perforation occurs when a small piece of bowel is drawn into the uterus with a curet. This, of course, necessitates laparotomy. The vast majority of perforations result in no remarkable complications, hence further procedure is unnecessary.

When care and thoroughness are exercised, dilatation and curettage provide one of the most informative gynecologic procedures, entailing a minimum of risk and secondary disability.

References

1. Hendricks, C. H.: Supracervical hysterectomy and carcinoma of cervix. J.A.M.A. **146**:100 (May 12) 1951.
2. Crossen, R. J.: Wide conization of cervix. Am. J. Obst. and Gynec. **57**:187 (Jan.) 1949.

CONGENITAL ANOMALIES OF THE GENITOURINARY TRACT AS CAUSE OF OBSCURE DISEASE

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CONGENITAL anomalies of the genitourinary tract are relatively common and are varied in type. They may be associated with symptoms directly related to the urinary tract and thus come to medical attention. However, they may be responsible for obscure symptoms and should be considered in differential diagnosis.

A detailed discussion of the embryology of the genitourinary tract is not necessary for clinical appreciation of these conditions. However a brief explanation may help to orient our thinking. The genital and urinary organs are closely related in embryologic development. Since both arise from the mesoderm of the intermediate cell mass which is the primordium of the urogenital system, there is a common relation of ducts of the urinary and genital organs with the primitive cloaca.

The metanephros or kidney consists of two portions: (1) the secretory or glandular, and (2) the collecting system. The glandulotubular portion which comprises the glomerulus and the other portions of the nephron or secretory unit arises from the metanephrogenic blastema; the collecting portion or ureter is an outgrowth from the primary excretory duct. Growing dorsocranially, it finally presses into the metanephrogenic blastema where, by division, it forms the renal pelvis, calyces, and collecting tubules of the kidney; finally, the tissue of the renal blastema forms its nephrons and the lumen of these becomes continuous with those of the collecting tubules.

Primitively the ureters open on the dorsal wall of the mesonephric duct. As development progresses, each acquires an independent opening into the vesicourethral primordium which becomes the bladder and urethra. If two ureteral buds develop simultaneously they may persist to form complete ureteral reduplication in which both ureteral orifices will open within the bladder. However, if a second ureteral bud develops at a later stage, it may be incorporated in that portion of the mesonephric duct which develops below the vesical outlet. In this way it may come to open into the urethra, ejaculatory duct, seminal vesical or vas deferens in the male or the urethra or vestibule in the female. Embryologists are a bit uncertain how the ureters may come to open into the vagina and uterus, although there are well established cases of this anomaly. It should be noted, also, that embryologically an ectopic ureter always goes to the upper portion of a duplex kidney. In the same manner, when two ureteral orifices are present within the bladder, the lowermost orifice always leads to the upper part of a duplex kidney.

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With these facts in mind, we may set down a working classification of the anomalies of the upper urinary tract.

Kidney

- Position—
  - Malrotation
  - Ectopia
- Form—
  - Fusion—horseshoe, crossed, etc.
  - Infantile—aplastic, multicystic
  - Congenital absence
  - Duplex—triplex
- Vascular—
  - Aberrant artery
  - Anomalous vessels

Ureter

- Division—
  - Reduplication (partial, complete)
    - To upper renal pelvis
    - Ending blindly
  - Triple ureters
- Failure of developments (neuromuscular?)
  - Megaloureter, unilateral, bilateral
  - Congenital diverticulum
- Ectopic opening—
  - Male: urethra, seminal vesicle, vas deferens
  - Female: urethra, vagina, cervix, uterus

Diagnosis

One must of course suspect the possibility of a congenital anomaly. A careful analysis of the history may present the first clue. Physical examination may yield few significant positive findings and perhaps none which will establish the final diagnosis. If there is pus in the urine, attention will be directed to the urinary tract. However, a negative urine does not exclude an anomaly. Likewise, other laboratory studies may be of limited value.

Adequate x-ray examination is essential. A plain roentgenogram of the abdomen should be made first and, following this, an intravenous urogram. This alone may establish the diagnosis, or it may be valuable in directing subsequent examinations. In viewing the urogram, there are certain things which should cause suspicion. Absence of dye in one kidney indicates further study. Sometimes there may be a larger renal shadow than can be supplied by the visible pelvis, an observation which may suggest duplex kidney, renal cyst, or tumor. Traces of dye should be looked for in abnormal locations and renal fusions of various types usually can be detected by a urogram. Dilated ureters or an atypical cystographic shadow may be noted also.

A careful cystourethroscopic examination should be included, and ureteral catheterization when indicated. When in search of a congenital anomaly, particularly an ectopic ureteral orifice, a detailed cystoscopic inspection is necessary. Frequently repeated examinations are required before a diagnosis can finally be made. In a suspected case a good rule is to probe every suspicious opening in the bladder or urethra with a ureteral catheter. Sometimes insignificant looking "dimples" will be the key to the correct diagnosis.

In some of the anomalies it may not be possible to establish a preoperative diagnosis and the exact nature of a suspected lesion may be disclosed only by surgical exploration.

FIG. 1. Case 2. Bilateral retrograde pyelogram showing hydronephrosis in left half of fused pelvic kidney.

In considering the differential diagnosis it should be remembered that congenital anomalies of the urinary tract may simulate various intra-abdominal lesions. Therefore, in any atypical case, no operation should be carried out until the urinary tract has been carefully excluded as the source of origin. This may save the patient a needless operation.

Symptoms

In this discussion we are concerned chiefly with those symptoms which would not ordinarily direct immediate attention to the urinary tract.

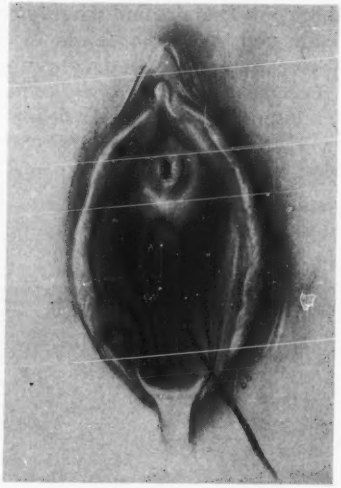


FIG. 2. Case 4. Showing location of ectopic ureter opening into vagina. Ureteral catheter has been passed into anomalous ureter.

Pain is an extremely variable symptom and there is no pain which can be said to be typical of any urinary tract anomaly. However, with any discomfort in the flank, lateral abdomen, or pelvis which is not characteristic of any other known disease and in which the entire clinical picture is not clear-cut, urinary tract investigation should be considered. The pain of a pelvic kidney may be confusing, especially in the woman, where it is usually mistaken for disease of the pelvic organs. In one of our patients the pain was thought to be due to a diverticulitis of the colon. The pain associated with certain ureteral anomalies may simulate almost any intra-abdominal lesion. If on the right side, the patient usually has had an appendectomy or a pelvic laparotomy before the true

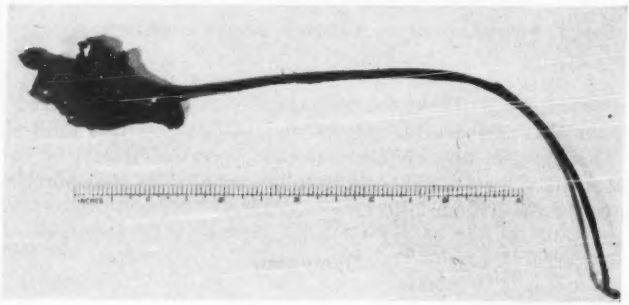


FIG. 3. Case 4. Gross specimen removed at operation.

nature of the condition is recognized. There being no characteristic pain, and since these patients almost never represent surgical emergencies, the careful physician, with the patient's interest in mind, will consider the possibility of a urinary tract anomaly and take measures to exclude this possibility.

Case Reports

Case 1. A man aged 34 complained of pain in the right groin and right side of the abdomen which had been associated with constipation. He had also observed that taking of an enema appeared to aggravate the abdominal pain. Colon x-ray disclosed no organic disease. Intravenous urogram revealed a normally functioning left kidney, but there was no dye in the region of the right kidney. There were traces of dye observed overlying the bones of the pelvis. Cystoscopy revealed a normal bladder. Retrograde right pyelogram disclosed the presence of a typical pelvic kidney with slight hydronephrosis. The patient was managed conservatively for a period of some 6 months, but the pain continued and became even worse. A transperitoneal nephrectomy was carried out. This resulted in relief of his symptoms. It should be noted that, in this case, the original urinalysis was entirely normal.

Case 2. A young man aged 28 was first observed complaining of attacks of sudden acute abdominal pain, beginning in the back and radiating through to the deep pelvic region. The attacks occurred about every 2 months at the onset, but became more frequent and severe. Recently he had experienced fever and sweating. Some intra-abdominal disease was suspected. He had had his appendix removed when a child of 12 because of indefinite lower abdominal pain.

On physical examination considerable tenderness was evident in the lower part of the abdomen, with an indefinite rounded mass perceptible in the midline. Intravenous urogram showed prompt function from the right kidney, which was low-lying and of atypical pelvic outline. No dye could be seen in the region of the left kidney. A retrograde pyelogram revealed the presence of a hydronephrosis in the left pelvic kidney which appeared to be fused to the right kidney (fig. 1).

Nephrectomy of the hydronephrotic left half of this fused pelvic kidney completely relieved the patient's symptoms. He later developed an obstructing stone in the right ureter, which was removed by ureterolithotomy. Since that time the patient has experienced no further difficulty.

Case 3. A young woman, 29 years of age, presented the complaint of recurrent severe attacks of pain in the lower right abdomen associated with intense vomiting. The onset had been 6 years previous to the present examination. An initial diagnosis of appendicitis had been made and appendectomy performed. Her symptoms recurred and because of the presence of a slight icterus, gall bladder disease was suspected and a cholecystectomy performed. This afforded no relief of her symptoms and at a later date pelvic laparotomy was done and a salpingo-oophorectomy performed for a supposed ovarian cyst. Her symptoms continued, however, with recurring bouts of pain, vomiting, and considerable weight loss and she was referred to the Clinic for further study.

Urinary tract investigation was carried out. Intravenous pyelogram showed the left kidney to be normal. The right kidney revealed a small pelvis which, in other respects, was normal. Cystoscopy examination disclosed the presence of two ureteral orifices on the right. The upper orifice was catheterized and retrograde pyelogram filled the small renal pelvis, lying in normal position. The lower ureteral orifice was catheterized, but the catheter could be passed only 3 or 4 cm. at which point the patient complained

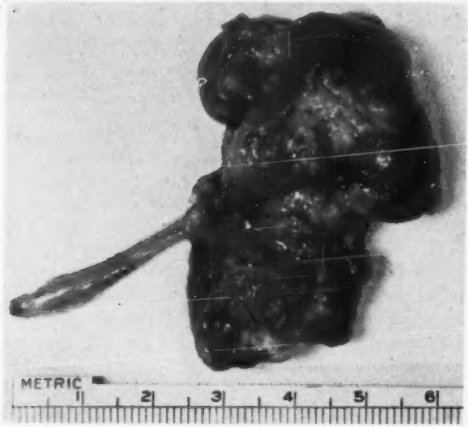
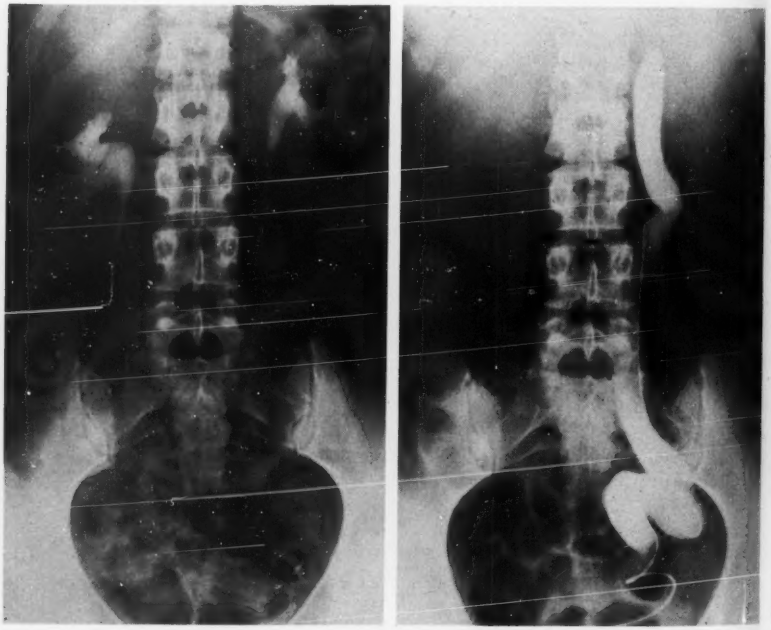


FIG. 4. Case 5. Gross specimen removed at operation showing congenital multicystic kidney.

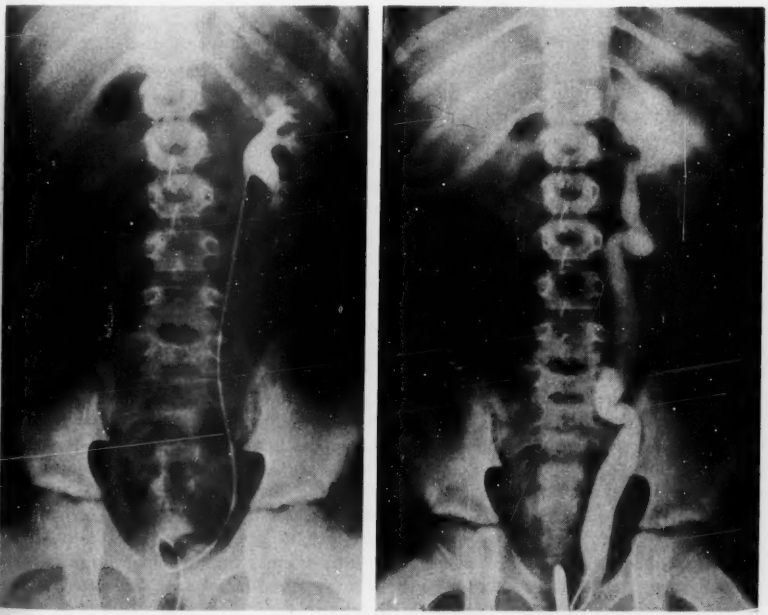


(a) (b)

FIG. 5. Case 6. (a) Intravenous urogram showing essentially normal renal pelves. However, left kidney appears smaller than right. (b) Ureteral catheter passed into vaginal opening with injection of pyelographic media showing dilated tortuous ectopic ureter on left side. Infection was present.

of pain similar to the type she had been experiencing. Attempts to fill this ureter were unsuccessful because of the intense pain. Operation was performed and an anomalous accessory ureter was found which ended blindly at the level of the hilus of the kidney. Removal of this accessory ureter completely relieved the patient of her symptoms. This case has been previously reported.[1]

Case 4. A woman of 31 came to the Clinic complaining of severe right lower quadrant pain which was referred to the right lumbar region and the inner surface of the right thigh. The history revealed that since the age of 11 she had experienced attacks of right lower quadrant pain, occasionally associated with nausea and vomiting. An appendectomy had been performed 11 years previously because of a severe bout of right lower quadrant pain accompanied by fever, nausea, and vomiting. However, the pain was not relieved and she continued to experience similar attacks. Later she underwent a pelvic laparotomy and uterine suspension was done with curettage and conization of the cervix. Because her symptoms continued, a left oophorectomy was performed without relief of symptoms, and 2 years previous to this examination a complete hysterectomy, which failed to relieve her pain. Careful questioning revealed the fact that she had periodic vaginal discharge and she believed that this discharge increased in amount following her attacks of pain. There was also a history of severe dyspareunia.



(a) (b)

FIG. 6. Case 7. (a) Retrograde left pyelogram showing apparently normal left kidney pelvis. (b) Catheter passed into ectopic ureter opening into urethra. Injection of pyelographic dye shows marked hydroureter and hydronephrosis of upper pelvis of duplex kidney.

As part of the investigation, intravenous urography was done, revealing no function from the right kidney. The left kidney functioned normally and presented some compensatory hypertrophy. The patient had considerable vaginal discharge and on careful examination a small reddened area was found in the right anterior vaginal wall about 2.5 cm. back of the urethral meatus. After several attempts a small No. 4 ureteral catheter passed into this opening and progressed for a distance of about 20 cm. (fig. 2). Injection of radiopaque dye revealed an atypical smudge of dye extending between the transverse process of the second and third lumbar vertebrae. At operation the anomalous ureter was identified and on tracing it upward, it was found to end in a small mass of infected atrophic and partially cystic renal tissue. The patient was relieved of her symptoms (fig. 3).

Fever of unexplained origin with or without chills should always direct attention to the urinary tract. When shown to be the source of the difficulty pyuria will usually be present although not necessarily. In the case of an infected ectopic ureter the opening may be outside the bladder, permitting the urine to remain clear. Also, as will be demonstrated in a subsequent case, an infected cyst or multicystic kidney may produce fever and yet reveal little if anything indicative in the urine.

Case 5. A child of 32 months was brought to the Clinic because of intermittent periods of fever of undetermined origin. The present illness was of some 9 days' duration, during which time she had had daily temperature elevation to 102 and 103 F. The patient had become listless although there were no localizing symptoms. As a part of the general survey, intravenous urography was done which showed a normally functioning left kidney but no dye visible on the right side.

The urine analysis had been essentially negative. However, further investigation was indicated because of the absence of function of the right kidney.

A cystoscopic examination was carried out, which showed the bladder to be essentially normal. A ureteral orifice was present on the right side. A No. 4 catheter entered the orifice but would not pass beyond approximately 6 cm. An attempt to inject pyelographic media showed no dye at all in the kidney and all dye refluxed into the bladder.

Exploration of the right kidney was carried out. At operation a congenital multicystic type of kidney with atresia of the upper ureter was found (fig. 4). Following removal the patient had an uneventful convalescence, and has experienced no recurrence of fever. She has remained well since operation.

Case 6. A married woman of 34 was admitted to the Clinic with the complaint of recurrent episodes of chills and fever associated with left flank pain. While she had experienced this discomfort for the past 10 years, episodes appeared to be occurring with increasing frequency. Especially significant was the fact that, subsequent to these episodes, there was a noticeable increase of vaginal discharge, from which Trichomonas had been isolated.

Intravenous urogram revealed an apparently normal upper urinary tract. Careful vaginal inspection disclosed the presence of a small reddened area well up on the left lateral vaginal wall, close to the cervix. A minute opening was finally located with a lacrimal duct probe, and after dilation a No. 4 catheter was passed into this opening for a distance of 25 cm. Injection of radiopaque media disclosed the presence of a dilated tortuous ectopic ureter, which ended blindly at the level of the upper pole of the left kidney (fig. 5). Of interest is the fact that material obtained from this ureter was pus-laden and contained many trichomonads.

Surgical removal of this lesion has afforded this patient complete relief of symptoms.

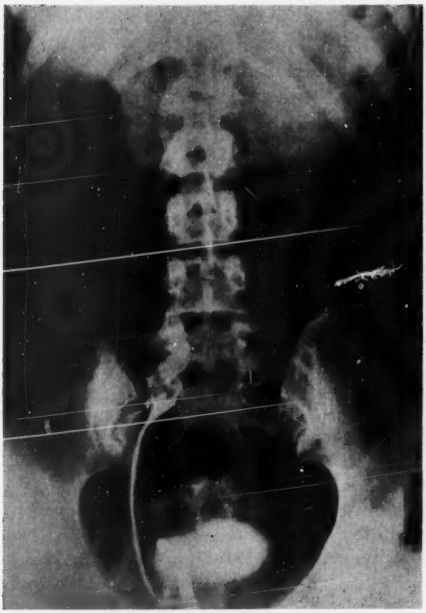


FIG. 7. Case 8. Retrograde right pyelogram showing small contracted pelvic kidney in patient with hypertension.

Case 7. A child, 8 years of age had experienced recurrent episodes of fever associated with pyuria. This had directed attention to the urinary tract. However, an intravenous urogram showed an apparently normal urinary tract.

A cystoscopy was carried out. The left ureter was catheterized and a retrograde pyelogram appeared essentially normal. However, the patient had a recurrence of pyuria at which time a recheck cystoscopic examination revealed the presence of an edematous area in the urethra just distal to the vesical neck, in the center of which there appeared to be a small opening. When probed with the urethral catheter, this was found to extend into the kidney area and a retrograde pyelogram revealed a definite hydronephrosis of the upper half of a duplex kidney on the left side with a nectopic ureteral orifice opening into the urethra (fig. 6).

A heminephrectomy and ureterectomy were carried out. The patient made an uneventful convalescence and has since remained well.

Atypical or intermittent vaginal discharge may be due to a urinary tract anomaly which almost invariably is due to an ectopic ureter emptying into the vagina. If this ureter is connected with functioning kidney tissue the patient usually presents the complaint of urinary incontinence; this possibility must always be considered in baby girls with suspected incontinence. However the ureter may end blindly, or end in a small mass of atrophic kidney, in which event vaginal discharge may be the chief symptom. This may be the source of

recurrent trichomonas vaginitis or other types of infections, as illustrated by the case previously presented.

Obscure perineal and rectal pain are symptoms which deserve careful urologic study. We have observed a case of a large congenital type of a cyst of the seminal vesical into which a blindly ending ureter emptied (reported case).[2]

Occasionally a complete survey for **hypertension** will disclose previously unsuspected urinary tract lesions. An intravenous urogram has become an almost routine examination in the study of hypertension and this examination should never be omitted in young people. The following case illustrates its importance.

Case 8. A young woman, 20 years of age, entered the Clinic with a history of hypertension, known to have been present for 4 months. There were no other complaints. The most significant finding on physical examination was the blood pressure, which varied from 210/115 to 174/104. The intravenous urogram showed a normally functioning left kidney. There was no dye visible on the right side in any of the films of the urogram series. A cystoscopy was carried out but showed a normal bladder. The right ureter was catheterized, but the catheter was passed only about 15 cm. A retrograde pyelogram revealed the presence of a small aplastic contracted pelvic kidney (fig. 7). A transperitoneal nephrectomy was carried out. The patient made an uneventful recovery following operation and since surgery the blood pressure has been maintained at nearly normal levels, ranging from 135/80 to 160/92 on postoperative visits.

Summary and Conclusions

In any obscure abdominal complaint a congenital anomaly of the genitourinary tract should be considered in the differential diagnosis. Careful urologic investigation should be carried out before subjecting the patient to a needless operation. Illustrative cases have been presented to call attention to some of these lesions and the varied symptomatology they may present. Many other types of congenital anomalies may be encountered.

References

1. Engel, W. J.: Aberrant ureters ending blindly. J. Urol. **42**:674 (Nov.) 1939.
2. Idem: Ureteral ectopia opening into seminal vesicle. J. Urol. **60**:46 (July) 1948.

NEWER CONCEPTS OF BLOOD COAGULATION

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THE fundamental concepts of blood coagulation formulated almost 50 years ago by Morawitz[1] have not changed significantly. The theory is simple but fails to explain three important features. These are the mode of action of the various substances involved in the clotting process, the origin of thromboplastin, and the function of platelets. During the past decade knowledge pertaining to the mechanism of blood coagulation has become increasingly complex.

Theory of Morawitz

I. **Calcium + thromboplastin + prothrombin ——→ thrombin**
II. **Thrombin + fibrinogen ——→ fibrin**

It now appears that prothrombin is converted to thrombin with the aid of conversion and accelerator factors from plasma and platelets, and that the formation of fibrin is enhanced by an accelerator from platelets.

Origin of Thromboplastin and the Function of Platelets

Morawitz's theory presumes the liberation of free thromboplastin as a preliminary step in clotting. Quick[2,3] states that thromboplastin still remains an undefined entity. Free thromboplastin is present in tissues. In plasma it exists as a precursor which is activated by an enzyme derived from platelets. This plasma precursor, thromboplastinogen, may be identical with the plasma fraction known as antihemophilic globulin which is lacking in hemophilia. Following the lysis of platelets, an enzyme called thromboplastinogenase is liberated, which activates thromboplastinogen in the plasma to thromboplastin. Thromboplastin then acts stoichiometrically with prothrombin complex to form thrombin. Most investigators agree that thromboplastin is of at least two varieties. One is a slower acting thermostable, fat soluble phospholipid and the other a thermolabile lipoprotein. Both have special functional differences which tend to supplement each other, resulting in a synergistic effect on the thromboplastic mechanism.

Fantl and Nance[4] and others[5,6] have reported an accelerator factor derived from platelet extract which hastens the formation of prothrombin to thrombin. The mechanism of action is similar to serum accelerator which is described subsequently, but the chemical characteristics of each are distinguishable.

Another platelet accelerator apparently enhances the reaction between fibrinogen and thrombin in the formation of fibrin as reported by Ware, Fahey and Seegers.[6]

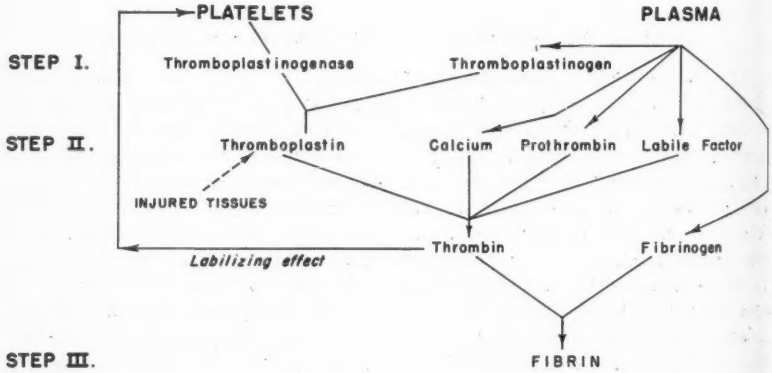
A serum vasoconstrictor agent which aids in the mechanism of hemostasis

appears to arise from platelet lysis and has been named serotonin by Rapport, Green and Page.[7]

Prothrombin Conversion and Accelerator Factors

A plasma factor responsible for variable prothrombic convertibility is not a new concept. In 1908 Nolf[8] described a substance necessary for the formation of thrombin which he called thrombogene. Smith[9,10,11] suggested this type of mechanism to explain deviations between the two stage and one stage tests for prothrombin. In 1943 Quick[12] proposed that prothrombin was a three component complex consisting of prothrombin A, prothrombin B and calcium. In 1947 Quick's[13] theory was changed and the term labile factor was substituted for prothrombin A which is the substance that disappears from stored oxalated blood. Prothrombin in human plasma (stable factor) exists partly free and partly in a precursor state according to Quick and Stefanini.[14] The factor responsible for activation to free prothrombin has not been identified. Calcium is apparently activated when it combines with labile factor and appears to react stoichiometrically in the formation of thrombin.

MECHANISM OF COAGULATION OF BLOOD ACCORDING TO QUICK[15]



In 1944 Owren[16] described a patient with severe bleeding, long prothrombin times and clotting times, yet with no apparent deficiency of prothrombin. In 1947 he[17] presented a classical discussion of the background for his concept of a new pair of clotting factors and was the first to show that an inactive factor becomes changed to another in the process of clotting. Factor V is described as the inactive plasma precursor of Factor VI. Its effect is to hasten the conversion of prothrombin to thrombin; it is normal in hemophilia and has no effect on the second stage of clotting. In Owren's [17] original paper, he suggests that Factor V reacts with prothrombin, thromboplastin and calcium

to form Factor VI which then reacts with prothrombin in the presence of calcium to form thrombin.

MECHANISM OF BLOOD COAGULATION ACCORDING TO OWREN[17]

STEP I. Factor V + Prothrombin ? $\xrightarrow{Ca + Thromboplastin}$ Factor VI

STEP II. Prothrombin $\xrightarrow{Factor\ VI + Ca}$ Thrombin

STEP III. Fibrinogen $\xrightarrow{Thrombin}$ Fibrin

Stefanini doubts the role of prothrombin in Step I.

In 1947 Ware, Guest and Seegers[18,19] segregated a globulin from prothrombin by differential ammonium sulfate solubility which hastened the conversion to prothrombin to thrombin and which, if sufficiently lacking, prevented the full conversion of prothrombin. The substance, believed to be a proenzyme, was designated prothrombin activator, hence the term Ac-globulin, which is probably inactive and requires only thrombin in low concentration for activation to serum Ac-globulin which acts as a catalyst in the formation of thrombin.

Ware, Fahey and Seegers[6] have confirmed the finding that platelet extract contains only a small amount of thromboplastin and that a substance is present which hastens the conversion of prothrombin to thrombin. This substance is called platelet accelerator. A second substance was found by these investigators which hastens the formation of fibrin from thrombin and fibrinogen and is designated platelet Factor II. Although this factor shows only moderate activity, failure to recognize its existence has probably resulted in faulty interpretation of experimental results.

Platelet accelerator requires no further activation and becomes effective when platelets rupture. It serves primarily to catalyze the initial formation of thrombin. Plasma Ac-globulin is activated by the first small amount of thrombin to serum Ac-globulin which becomes the main accelerator resulting in the rapid formation of thrombin. (Refer to next chart.)

Stefanini[21] has recently proposed a mechanism of blood coagulation in which he divides the reactions into slow and accelerated phases, thereby taking into account the common observation that normal blood shed in a glass tube remains fluid for several minutes and then quickly begins to solidify into a clot. The first phase includes a series of reactions until thrombin is formed. Once thrombin begins to form, the accelerated phase of blood coagulation begins. Thrombin autocatalytically excites its own production by labilizing more platelets resulting in the formation of more thromboplastin. Thrombin

METHOD OF BLOOD COAGULATION ACCORDING TO WARE AND SEEGERS [20]

STEP I. Prothrombin + Thromboplastin —(*Ca ++*; *platelet accelerator*)→ Thrombin

STEP II. Plasma Ac-globulin ——→ Serum Ac-globulin

STEP III. Prothrombin + Thromboplastin —(*Ca ++*; *platelet accelerator*; *Serum Ac-globulin*)→ Thrombin

STEP IV. Fibrinogen —(*Thrombin*)→ Fibrin

also activates the prothrombin conversion factor into a serum accelerator which is enhanced by a platelet accelerator in the formation of thrombin. Fibrinogen, considered a passive factor in coagulation, probably is influenced by a platelet factor and becomes quickly clotted.

HYPOTHETICAL REPRESENTATION OF THE MECHANISM OF COAGULATION OF BLOOD ACCORDING TO STEFANINI [21]

SLOW PHASE

STEP I. Thromboplastinogen (PLASMA)

Thromboplastinogenase (PLATELETS) ——→ Thromboplastin

STEP II. Prothrombin + Thromboplastin + Calcium +
Plasma prothrombin conversion factor ——→ Thrombin

ACCELERATED PHASE

STEP III. Plasma prothrombin conversion factor
(or other plasmatic precursor)

Thrombin ——→ Serum Accelerator

STEP IV Prothrombin + Thromboplastin
+ calcium —(serum accelerator; platelet accelerator)→ thrombin

STEP V Fibrinogen —(thrombin; platelet factor (?))→ Fibrin

Comparison of Prothrombin Conversion and Accelerator Factors

There is disagreement as to the mechanism by which conversion and accelerator factors participate in the formation of thrombin. Seegers[22] assumes that prothrombin contains all the building stones for the structure of the thrombin molecule and nothing needs to be derived from calcium, thromboplastin or other activators. Purified prothrombin reacts slowly in the presence of calcium and a concentrated thromboplastin solution due to absence of Ac-globulin which apparently acts as a catalyst. Ware and Seegers[20] believe that thrombin is a prerequisite to serum Ac-globulin formation.

$$\text{I. Plasma Ac-globulin} \xrightarrow{\text{thrombin}} \text{serum Ac-globulin}$$

According to Owren[17] Factor VI is produced by an autocatalytic reaction between prothrombin, Factor V, thromboplastin and calcium. Factor VI is believed to be the activator of prothrombin.

$$\text{I. Prothrombin (?)} + \text{Factor V} \xrightarrow{\text{thromboplastin} + \text{Ca}} \text{Factor VI}$$

$$\text{II. Prothrombin} \xrightarrow{\text{Factor VI} + \text{Ca}} \text{Thrombin}$$

Owren thus considers Factor VI to be a prerequisite to thrombin formation.

Quick and Stefanini[23] believe there is a direct quantitative relationship between labile factor present and the yield of thrombin from a definite amount of prothrombin suggesting a stoichiometric type of reaction.

According to Stefanini,[21] the various conversion factors, i.e., labile factor, Factor V and plasma Ac-globulin share similar properties and are probably identical. Controversy persists as to whether the action is simply catalytic or essential in the conversion of prothrombin to thrombin.

The function of accelerators requires further investigation. The liberation of platelet accelerator appears to set up the mechanism of blood coagulation. Serum accelerator evolves after the clotting process is under way. Evidence has accumulated that plasma contains a precursor of serum accelerator.

Seegers[24] states that the complexity of blood coagulation precludes the possibility of organizing a diagrammatic summary. Only controversial issues are presented herein. A discussion of physiologic anticoagulants and the fibrinolytic mechanism which inhibit intravascular thrombosis has been omitted. Seegers[24] has recently presented a review of this subject.

Summary

It has become increasingly apparent during the last decade that blood coagulation is a complex process. There is now general agreement that conversion and accelerator factors participate in the reaction. According to our present knowledge, thromboplastin, of tissue origin or of platelet origin or both, reacts with calcium and prothrombin to form minute amounts of thrombin. Platelet accelerator according to Seegers catalyzes the initial reaction. Plasma Ac-

globulin is activated by small amounts of thrombin to serum Ac-globulin. Rapid formation of thrombin results from the catalytic action of serum Ac-globulin and platelet accelerator. Platelet accelerator serves primarily to initiate the reaction while serum Ac-globulin becomes the major catalyst in the formation of thrombin. The reaction between thrombin and fibrinogen is probably hastened by a second platelet factor.

References

1. Morawitz, P.: Beitrage zur Kenntnis der Blutgerinnung. Deutsch. Arch f. klin. Med. **79**:1, 1904.
2. Quick, A. J.: Coagulation of blood and hemostasis. Ann. Rev. Physiol. **12**:248, 1950.
3. Idem: Modern concept of coagulation of blood. Marquette M. Rev. **13**:89 (April) 1948.
4. Fantl, P. and Nance, M. H.: Acceleration of thrombin formation by plasma component. Nature **158**:708 (Nov. 16) 1946.
5. Mann, F. D., Hurn, M. M. and Magath, T. B.: Observations on conversion of prothrombin to thrombin. Proc. Soc. Exper. Biol. and Med. **66**:33 (Oct.) 1947.
6. Ware, A. G., Fahey, J. L. and Seegers, W. H.: Platelet extracts, fibrin formation and interaction of purified prothrombin and thromboplastin. Am. J. Physiol. **154**:140 (July) 1948.
7. Rapport, M. M., Green, A. A. and Page, I. H.: Crystalline serotonin. Science **108**:329 (Sept. 24) 1948.
8. Nolf, P.: Contribution a l'etude de la coagulation du sang. Arch. Int. Physiol. **6**:115, 1908.
9. Owen, C. A., Hoffman, G. R., Ziffren, S. E. and Smith, H. P.: Blood coagulation during infancy. Proc. Soc. Exper. Biol. and Med. **41**:181 (May) 1939.
10. Warner, E. D., Brinkhous, K. M. and Smith, H. P.: Plasma prothrombin levels in various vertebrates. Am. J. Physiol. **125**:296 (Feb.) 1939.
11. Idem: Prothrombin conversion rate in various species. Proc. Soc. Exper. Biol. and Med. **40**:197 (Feb.) 1939.
12. Quick, A. J.: On constitution of prothrombin. Am. J. Physiol. **140**:212 (Nov.) 1943.
13. Idem: Components of prothrombin complex. Am. J. Physiol. **151**:63 (Nov.) 1947.
14. Quick, A. J. and Stefanini, M.: State of component A (prothrombin) in human blood. J. Lab. and Clin. Med. **34**:1203 (Sept.) 1949.
15. Quick, A. J.: Pediatric aspects of hemophilia. Pediatrics **3**:312 (March) 1949.
16. Owren, P. A.: Arbok for det Norske Videnskoprakademi. p. 21, 1944.
17. Idem: Coagulation of blood; investigations on new clotting factor. Acta med. Scandinav. Supp. 194, p. 1, 1947.
18. Ware, A. G., Guest, M. M. and Seegers, W. H.: Factor in plasma which accelerates activation of prothrombin. J. Biol. Chem. **169**:231 (June) 1947.
19. Idem: Plasma accelerator factor and purified prothrombin activation. Science **106**:41 (July 11) 1947.
20. Ware, A. G. and Seegers, W. H.: Serum Ac globulin. Am. J. Physiol. **152**:567 (March) 1948.
21. Stefanini, M.: Conversion factors and accelerators in formation of thrombin. Blood **6**:84 (Jan.) 1951.
22. Seegers, W. H. and Ware, A. G.: Recent advances in our knowledge of prothrombin. Am. J. Clin. Path. **19**:41 (Jan.) 1949.
23. Quick, A. J. and Stefanini, M.: Nature of action of labile factor in formation of thrombin. Am. J. Physiol. **160**:572 (March) 1950.
24. Seegers, W. H.: Blood coagulation. In Sumner, J. B. and Myrback, K.: The Enzymes, vol. 1, part 2. New York, Academic Press, 1951, p. 1106.

VEGETATIVE ENDOCARDITIS DUE TO HISTOPLASMA CAPSULATUM

Report of a Case

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HISTOPLASMA capsulatum was first recognized by Darling[1] in 1906 as being pathogenic for man. The organism most commonly causes a benign pulmonary infection which is not accompanied by symptoms and progresses to healing with calcification. Generalized infection occurs at times, however, and in these instances the fungus usually affects the reticuloendothelial system predominantly. Involvement of the heart is of rare occurrence, 9 cases having been reported to date.[2,3,4,5,6,7,8,9,10] In 6 cases the pathologic lesions were those of an infective endocarditis, and in 2 the organisms were present only in the myocardium. In one the exact site of involvement was not mentioned. An additional case of vegetative endocarditis due to Histoplasma capsulatum is recorded in this report.

Report of Case

A white, married woman, 55 years of age, was admitted to the hospital on November 18, 1949 because of intermittent fever, a mildly productive cough, anorexia and weakness of 2 months' duration. Periods of palpitation had been experienced for several months, but there had been no symptoms of myocardial failure. She had been receiving digitalis for 3½ weeks. There was a past history of rheumatic fever at the age of 8 years.

Physical examination revealed a poorly nourished patient in no acute distress. The temperature was 99 F., the heart rate 60 per minute, and the blood pressure 128 mm. systolic and 80 mm. diastolic. There were no petechiae, and no enlarged lymph glands were noted. The lungs were clear on percussion and auscultation. The area of relative cardiac dullness extended 10 cm. to the left of the midsternum in the fifth intercostal space. Auricular fibrillation was present. A blowing systolic and rumbling diastolic murmur of moderate intensity was audible at the apex. The liver was not enlarged or tender but the tip of the spleen was palpable just below the costal margin. There was no peripheral edema.

The urinalysis and blood count revealed no abnormalities except for a slight increase in the percentage of polymorphonuclear neutrophils in the differential count. The Wassermann reaction of the blood was negative. The erythrocyte sedimentation rate was normal. X-ray examination of the chest revealed moderate enlargement of the heart with prominence of the pulmonary artery and, in the right oblique view, enlargement of the left auricle. The lung fields were clear. An electrocardiogram confirmed the pres-

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ence of auricular fibrillation and showed depression of the RS-T segments in the standard limb leads and precordial leads.

During the first 4 days in the hospital the temperature did not exceed 99.6 F. but on the fifth day it rose abruptly to 103.2 F. From then until the patient's discharge to her home on January 4, 1950, an irregular fever of 100.4 F. to 102.4 F. occurred almost daily. Five blood cultures failed to yield organisms. The leukocyte count ranged from 4,800 per cu. mm. to 6,900 per cu. mm. Repeated measurements of the erythrocyte sedimentation rate gave normal results. A smear of sternal bone marrow revealed no abnormal cells and no organisms. Three specimens of sputum were examined and all were negative for tubercle bacilli and fungi. Intensive antibiotic therapy with penicillin, streptomycin and aureomycin had no effect upon the fever.

Further roentgenograms of the chest on the eleventh day in the hospital showed irregular infiltration in the middle and lower lobes of the right lung. There had been no change in the severity of the cough, no pain and no hemoptysis. The x-ray findings cleared gradually during the following 2 weeks.

The patient was discharged to her home unimproved 47 days after admission. During hospitalization her weight had decreased from 94 pounds to 88 pounds. After being home 5 weeks she was readmitted to the hospital in a mentally confused state and complaining of pain in the lower left quadrant of the abdomen and left flank which had developed 2 days earlier. During the time at home the low grade fever, anorexia and cough had continued, and the patient had become progressively weaker.

Physical examination revealed a cachectic, dehydrated, irrational and stuporous patient. The temperature was 101.8 F., the heart rate 104 per minute, the respiratory rate 20 per minute, and the blood pressure 100 mm. systolic and 80 mm. diastolic. There was a generalized light brown pigmentation of the skin which did not involve the mucous membranes of the mouth. No petechiae were present, and there was no lymphadenopathy. The cardiac findings were unchanged, and the lungs were clear on percussion and auscultation. The spleen was palpable as before. The erythrocyte count was 5,470,000 per cu. mm., and the hemoglobin content of the blood was 14.5 Gm. The white blood cell count was 15,400, and differential counts showed 87 per cent polymorphonuclear neutrophils. The urine contained one plus albumin, an occasional pus cell and a rare red blood cell.

The daily administration of fluids by intravenous injection resulted in improvement in the mental state but the patient's condition otherwise remained unchanged. On the fifth day in the hospital, she experienced sudden severe pain in the precordial area accompanied by increased weakness and the appearance of numerous medium rales over the base of both lungs. Twenty-four hours later severe pain recurred, this time in the substernal region. Profound shock developed almost immediately, and the patient died within a few minutes.

Necropsy. The heart weighed 490 Gm. The leaflets of the mitral valve were fused, thickened and extensively calcified, and the orifice of the valve was greatly reduced and of the "fish-mouth" type. The chordae tendineae were thickened, fused and shortened. On the auricular surface of the valve there was an irregular, flattened, somewhat granular, firm but friable, brownish-yellow vegetation which measured nearly 2 cm. in diameter (fig. 1). All other valves were normal. A small mural thrombus was present in the right ventricle. There was a small fresh infarct in the lower lobe of the left lung. The spleen weighed 450 Gm. and contained one large and several small infarcts. Several recent infarcts, ranging up to 1.4 cm. in diameter, were present in both kidneys. The adrenal gland appeared normal on inspection but microscopic examination showed small foci in which the cortical cells were replaced by histiocytes, lymphocytes and rather large oxyphilic cells.

FIG. 1. Vegetative endocarditis due to Histoplasma capsulatum showing the vegetation on the auricular surface of the thickened, stenosed mitral valve.

In one of four sections of the vegetation on the mitral valve, microscopic examination revealed small collections of histiocytes containing many round, sharply outlined bodies, measuring approximately 3 microns in diameter (fig. 2). These bodies were amphophilic with Gram-Weigert stain and were readily identified as Histoplasma capsulatum. Similar bodies could not be found in the lungs, liver, spleen or adrenal glands.

Cultures of the heart blood and from the vegetation remained sterile.

The pathologic diagnosis was (1) rheumatic heart disease with mitral stenosis, and (2) vegetative endocarditis due to Histoplasma capsulatum.

Discussion

Although it was suspected early in the clinical course that the patient might be suffering from subacute bacterial endocarditis, this diagnosis was discarded because of the consistently negative blood cultures and the lack of response to antibiotic therapy. A definite conclusion as to the cause of the fever was not arrived at during the patients's life. After the postmortem discovery of vegetative endocarditis, the failure to culture organisms from the heart blood and vegetation left the etiology of the infection still in doubt. It was only after the demonstration of Histoplasma capsulatum in the section from the vegetation that the cause of the illness was established. It is to be regretted that the possibility of histoplasmosis was not considered in the differential diagnosis so that a complement fixation test and histoplasmin skin test might have been done. Christie and his associates[11] have reported encouraging results from use of the ethyl ester of

FIG. 2. Histologic section of the vegetation on the mitral valve showing histiocytes containing Histoplasma capsulatum (x850).

vanillic acid in the treatment of histoplasmosis, and it would have been of interest to have employed the preparation in this instance.

The purpose of the present report is to emphasize again that Histoplasma capsulatum is a rare cause of vegetative endocarditis. The possibility of an infection of this type should be considered whenever a case of probable subacute bacterial endocarditis fails to yield positive blood cultures and does not respond to antibiotic therapy.

Summary

A case of vegetative endocarditis due to Histoplasma capsulatum is reported in a patient who had chronic rheumatic heart disease with mitral stenosis and insufficiency.

The possibility of an infection of this type should be considered whenever a case of probable subacute bacterial endocarditis fails to yield positive blood cultures and does not respond to antibiotic therapy.

References

1. Darling, S. T.: Protozoon general infection producing pseudotubercles in lungs and focal necrosis in liver, spleen and lymph nodes. J.A.M.A. **46**:1283 (April 28) 1906.
2. Parsons, R. J. and Zarafonetis, C. J. D.: Histoplasmosis in man; report of 7 cases and review of 71 cases. Arch. Int. Med. **75**:1 (Jan.) 1945.
3. Riehl, G.: Durch pathogene Sprosspilge bedingte Granuloma. Arch. f. Dermat. u Syph. **148**:392, 1925.

4. Agress H. and Gray, S. H.: Histoplasmosis in reticuloendothelial hyperplasia. Am. J. Dis. Child. **57**:573 (March) 1939.

5. Wood, W. B., Jr. and Moore, R. A.: Case reports of Barnes Hospital, case 22. J. Missouri M. A. **40**: 251 (Aug.) 1943.

6. Humphrey, A. A.: Reticuloendothelial cytomycosis (Histoplasmosis of Darling). Arch. Int. Med. **65**:902 (May) 1940.

7. Broders, A. C., Dochat, G. R., Herrell, W. E., and Vaughn, L. D.: Histoplasmosis producing vegetative endocarditis. J.A.M.A. **122**:489 (June 19) 1943.

8. Kemper, J. W. and Bloom, H. J.: Histoplasmosis; report of case. J. Oral Surg. **2**:167 (April) 1944.

9. Beamer, P. R., Reinhard, E. H. and Goodof, I. I.: Vegetative endocarditis caused by higher bacteria and fungi; review of previous cases and report of 2 cases with autopsies. Am. Heart J. **29**:99 (Jan.) 1945.

10. Kuzma, J. F.: Histoplasmosis, pathologic and clinical findings. Dis. Chest **13**:338 (July-Aug.) 1947.

11. Christie, A., Middleton, J. G., Peterson, J. C. and McVickar, D. L.: Treatment of disseminated histoplasmosis with ethyl vanillate. Am. J. Dis. Child. **80**:874 (Nov.) 1950.

DIAGNOSIS AND TREATMENT OF AORTIC RINGS

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AORTIC rings constitute a functionally important group of anomalies of the aortic arch which may compress the trachea, esophagus, or both. Many are amenable to surgical correction. It is our purpose to present the available methods by which they may be recognized, and to discuss the problems involved in treatment.

Edwards[1] has presented a logical and complete classification of the possible anatomic variants of the aortic arch system, based upon his recognition of the fact that a functioning double aortic arch exhibits the most complete adult representation of the six embryonic arches. From this basic pattern he classified the reported anomalies, and predicted others, on the premise that atresia of either arch at any given level would cause a specific anatomic variant of the complete pattern.

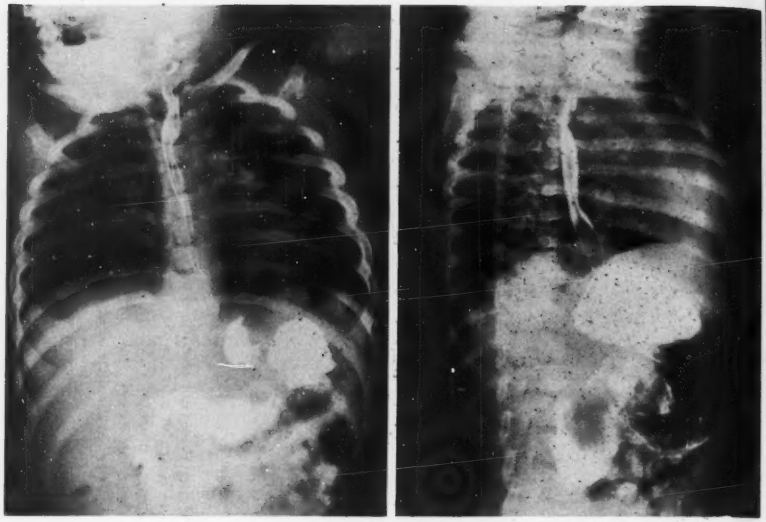
We believe that a simpler clinical classification, derived from that of Edwards, is useful in the practical approach to the recognition of these anomalies. We have limited the scope of the classification to those elements which are clinically recognizable in the living patient. In our experience it has led to reasonably precise preoperative evaluation of the problems encountered. Its usefulness depends upon the physician's ability to locate the position of the upper portion of the descending aorta. In each group the fundamental pattern is an anterior aortic arch with the descending aorta on the homolateral side. This is the normal structure of the aorta when it occurs on the left, and when seen on the right it is simply the mirror image of the normal pattern. In each group two other clinically recognizable and functionally important variants occur, which may compress the trachea or esophagus.

Group 1. Left descending aorta
- a. Left aortic arch (normal adult aorta).
- b. Left aortic arch with right subclavian artery arising from descending aorta distal to the left subclavian artery.
- c. Functioning right aortic arch, with or without atresia of the left aortic arch. If the left arch is patent a true double arch is present.

Group 2. Right descending aorta
- a. Right aortic arch (mirror image of normal aorta).
- b. Right aortic arch with left subclavian artery arising from descending aorta distal to the right subclavian artery.
- c. Functioning left aortic arch, with or without atresia of the right aortic arch. If the right arch is patent a true double arch is present.

(a) (b) (c)

FIG. 1. Fourteen month old girl, weight 15 pounds. Recurrent severe pneumonitis with temperature elevation to 106 F., accompanied by severe dyspnea and cyanotic attacks. (a) Apparently normal barium swallow with infant in upright position. (b) Large oblique esophageal defect caused by retroesophageal right subclavian artery; film made with child in supine position. (c) Right oblique view showing anterior displacement of esophagus at level of aortic arch.



(a) (b)

FIG. 2. (Same case as figure 1). Postoperative films in supine position after resection of anomalous right subclavian artery. (a) Posteroanterior view showing normal esophageal pattern. The left aortic arch and descending aorta displace esophagus to right of midline. (b) Normal posterior displacement of esophagus at level of aortic arch in the right oblique view.

The normal left aortic arch crosses transversely from right to left anterior to the trachea and descends on the left side. All of its branches arise anterior to the trachea and no compression is produced.

The most frequently encountered deviation from this normal pattern is the presence of a right subclavian artery having its origin from the upper posteromedial aspect of the left sided descending aorta, distal to the origin of the left subclavian artery. From this point it passes upward and to the right behind the esophagus to reach the right axilla. The characteristics of this anomaly are illustrated in figures 1 and 3. Occasionally the anomalous subclavian artery may pass to the right axilla between the trachea and esophagus and infrequently it crosses to the right in front of the trachea. When such a vessel exists there is, of course, no innominate artery on the right side, and the first branch from the aortic arch is the right common carotid.

When the aortic arch opposite the side of the descending aorta persists as a functioning structure it crosses the midline posterior to the esophagus. Thus, a functioning right aortic arch passes above the right main bronchus to the right of the trachea and esophagus, then crosses behind the esophagus to reach its junction with a left descending aorta. When both aortic arches persist as functioning structures, the left passes anteriorly across the trachea in its usual position, and the right passes posteriorly behind the esophagus as described.

The left is usually the smaller of the two arches, and a segment is often completely atresic; the right arch is seldom smaller.

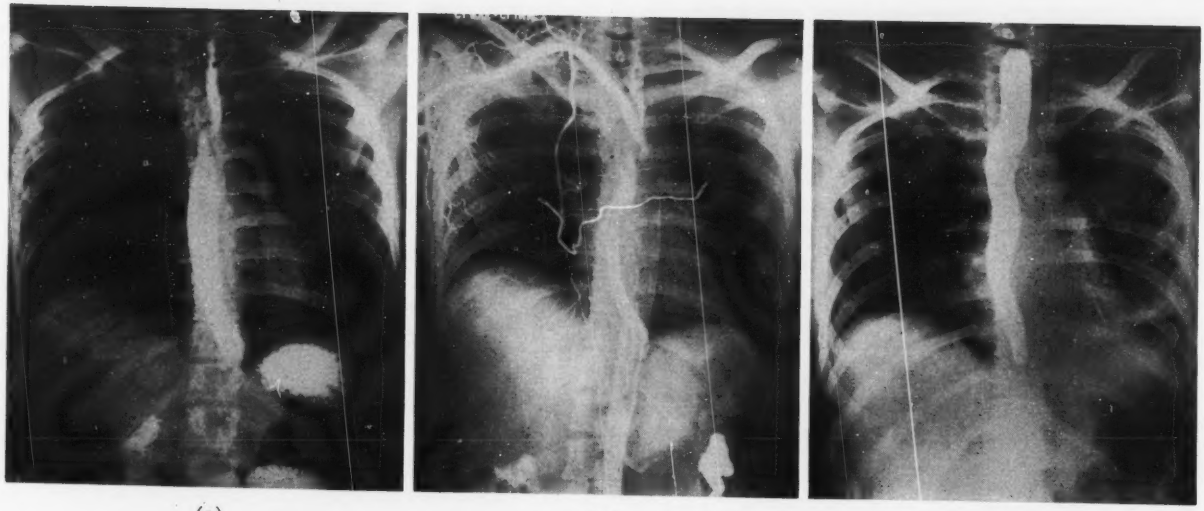
When the upper part of the descending aorta is displaced to the right side of the esophagus, the mirror images of the patterns previously described occur. The anomalies in this group are encountered less frequently than are those in the first group. Examples of each have been reported, however. The right arch crosses above the right main bronchus anteriorly to reach the right descending aorta, and no compression results. An anomalous left subclavian artery may arise as the fourth branch of a right aortic arch and right descending aorta. Such a vessel will cross upward behind the esophagus from right to left to reach the left shoulder (fig. 4). A functioning left aortic arch will pass to the left and posteriorly above the left main bronchus, and then turn sharply to the right behind the esophagus to join the descending aorta. If both arches persist, the left is the retroesophageal vessel, while the right is the anterior segment. An anomaly of this group is illustrated in figure 5.

Persons with aortic rings which cause a large amount of pressure on the trachea or esophagus will develop symptoms shortly after birth. In many experiencing less severe compression, symptoms may not appear until advanced age has been reached, when degenerative changes lead to widening of the aortic arch and its branches. Seldom will a young adult present definite evidence of compression. When such symptoms exist in this age group they may strongly suggest the presence of globus hystericus, and the patient may suffer for many years with a diagnosis of functional disease.

In infancy partial occlusion of the trachea often results in almost constant stridor. It is manifested by noisy inspiratory and expiratory sounds which are aggravated when the child is awake and excited and are much less pronounced during sleep. More frequently the most important functional embarrassment is caused by pressure upon the esophagus which leads to repeated episodes of regurgitation, followed by aspiration of food and mucus into the bronchial tree. The resulting pulmonary atelectasis and pneumonitis are the commonest causes of death.

Esophageal compression is especially dangerous during the first months of life when control of deglutition is most poorly developed. For this reason the most dangerously ill patients are often those in whom the nature of the lesion is hardest to define. Of 19 infants under 2 years of age reported in the review by Griswold and Young,[2] 14 died as a result of the lesion, 3 survived successful surgery and 2 died of causes not related to the anomaly. The acute pulmonary complications occurring in this age group draw attention to the lungs while the basic vascular lesion may be overlooked. Constricting anomalies of the aortic arch do not produce significant heart murmurs and there is no cause for cardiomegaly. The dramatic picture of cough, labored breathing, fever, paroxysmal attacks of cyanosis, and radiologic evidence of atelectasis or pneumonitis is dominant.

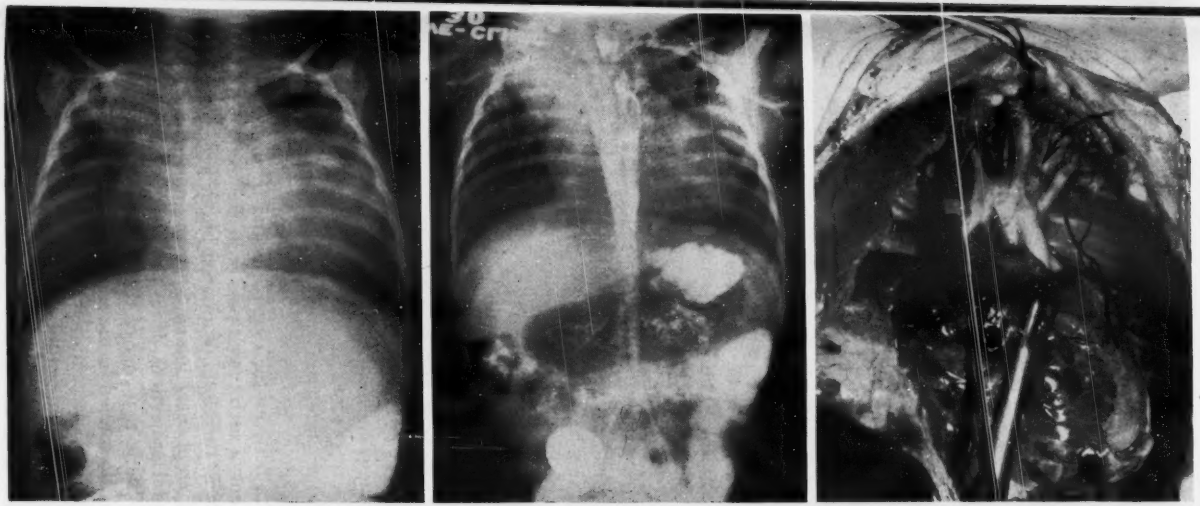
In older children and adults there may be a history of respiratory difficulties during infancy, but most often the lesion is asymptomatic. Occasionally there is dysphagia, particularly with ingestion of solid foods. Patients beyond middle age may develop this symptom, or persistent hoarseness.



(a) (b) (c)

FIG. 3. Thirty-three year old woman with persistent dysphagia since adolescence. No pulmonary symptoms. (a) Posteroanterior view reveals oblique filling defect in barium-filled esophagus. Esophagus displaced to the right; aortic knob poorly defined. (b) Retrograde aortogram from right brachial artery demonstrates right subclavian artery crossing esophagus posteriorly to its origin from left descending aorta. Note relation of descending aorta to barium-filled esophagus. (c) Normal esophageal pattern demonstrated postoperatively.

operatively.



(a) (b) (c)

FIG. 4. Twenty week old girl, weighing 6 pounds. Intractable pneumonitis cough, fever, labored breathing, intermittent cyanosis, failure to gain weight. (a) Chest x-ray demonstrating right upper lobe pneumonitis with atelectatic changes in the left upper lobe. (b) Retrograde aortogram from left brachial artery demonstrates left subclavian artery arising anomalously from right descending aorta; produces oblique filling defect in barium-filled esophagus, which is displaced to the left. Descending aorta to right of esophagus is well visualized. (c) Postmortem specimen shows right aortic arch crossing the trachea anteriorly to join right descending aorta. First branch on the left of the trachea (marked by arrow) is left common carotid. Right common carotid arises to the right of trachea. Vessel arising from distal arch is right subclavian artery. Left subclavian artery arises from posterior aspect of upper descending aorta, and is shown here passing around probe which is displacing the origin of vessel anteriorly into view.

When stridor or recurrent acute lower respiratory symptoms suggest the possibility of an anomaly of the aortic arch in infancy, it is usually a simple matter to confirm the presence or absence of the gross lesion. The definitive diagnosis of the abnormality is much more difficult. Without adequate preoperative knowledge of the anatomic structures any surgical attempt at correction is essentially an exploratory procedure, and the literature is replete with accounts of difficulties encountered at operation when only incomplete or fragmentary preoperative diagnoses were possible.[3,4]

Observation by fluoroscopy of the barium or lipiodol-filled esophagus is the simplest and most informative method available for detecting the presence of an anomaly of the aortic arch. Arkin,[5] Neuhauser,[6] and others have described ordinary deviations from the normal esophageal pattern.

The normal left arch and descending aorta do not impinge upon the posterior surface of the esophagus at the level of the aortic arch. In the posteroanterior view there is lateral displacement of the escophagus toward the right, and a slight filling defect is usually seen on the anterior surface of the esophagus in the right anterior oblique view at the level of the arch. The aortic knob is easily visualized in adults on the left side, though it may be difficult to recognize in infants and small children. The left descending aorta displaces the esophagus slightly to the right of the midline in its upper half so that, in the absence of mediastinal shift, the esophagus appears to be closer to the right border of the spine in the posteroanterior view than to the left.

The mirror image of this pattern is produced by a right aortic arch and descending aorta. The aortic knob, if visible, is present on the right side, although it is often obscured by the shadow of the superior vena cava. No posterior filling defect is seen, and the anterior filling defect is usually more prominent in the left anterior oblique than in the right oblique view. In the posteroanterior view the esophagus is displaced to the left at the level of the aortic arch, and the upper half of the esophagus appears closer to the left border of the spine than to the right.

The retroesophageal segment of constricting anomalies of the aortic arch produces a filling defect on the posterior aspect of the esophagus, displacing it anteriorly; this should always be evident on careful observation. The rare exceptions to this rule are instances when an anomalous subclavian artery arises as the fourth branch of the aortic arch and passes to the axilla on the side opposite the descending aorta between the esophagus and trachea, or anterior to the trachea. Ninety per cent of such vessels pass posterior to the esophagus,[7] and are easily recognized. It is, therefore, of greatest importance to study the appearance of the opacified esophageal lumen, with the patient lying down, in both oblique and the lateral projections. If no anterior displacement of the esophagus exists, it is improbable that any of the anomalies under consideration exist. The patient must be studied in the supine position, since occasionally an important defect will escape recognition if the study is made with the patient upright (figs. 1 and 2). Barium outlines the esophagus more effectively than does lipiodol, though if a tracheoesophageal fistula is suspected in an especially young infant, the danger of barium aspiration outweighs this con-

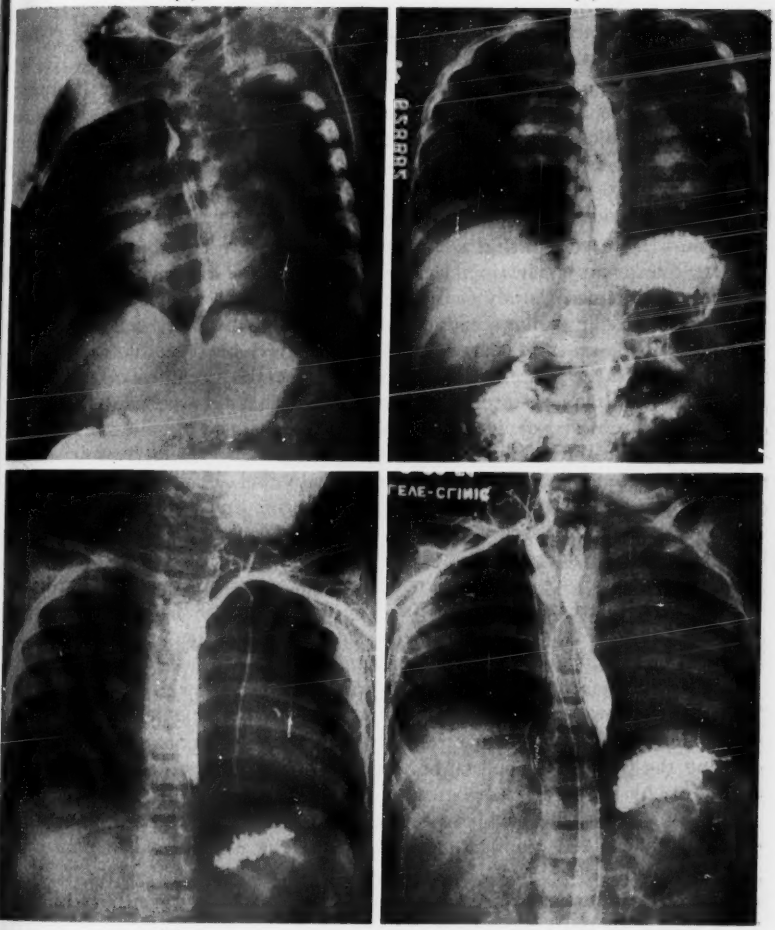


FIG. 5. Twenty-two month old boy had repeated severe episodes of pneumonitis, accompanied by severe dyspnea and cyanosis. (a) Left oblique view showing anterior displacement of barium-filled esophagus at level of aortic arch, indicating presence of a retroesophageal vessel. (b) Barium-filled esophagus visualized in posteroanterior view. Oblique filling defect crosses esophagus from low on right toward left shoulder. Above this there is indentation of esophagus toward right, and below the oblique defect esophagus appears to be displaced toward left. (c) Retrograde aortogram from left brachial artery demonstrates that left subclavian artery does not cross esophagus and therefore does not cause the oblique filling defect seen in (a) and (b). Beneath the barium column immediately above left diaphragm the descending aorta is visible and is displaced to the right of usual position. (Compare with figure 3b). (d) Retrograde aortogram from right brachial artery demonstrates a right innominate artery which does not cross the midline and faintly demonstrates right descending aorta below esophageal deformity. This would appear to be a left aortic arch with retroesophageal segment crossing to join right descending aorta.

sideration. Small quantities should be used in order to diminish the possibility of aspiration and to avoid overdistention of the esophagus, which will prevent easy recognition of a pressure defect.

Partial occlusion of the trachea may be demonstrated by instillation of lipiodol into the trachea or by bronchoscopy in instances where this is suspected. Plain lateral and posteroanterior films may suggest narrowing of the trachea above the bronchial bifurcation when no significant narrowing is actually present. When occlusion is suggested by history or routine x-ray study, the question should be resolved by one of the more definitive technics.

Although we believe that we can recognize the presence of esophageal deformity due to an aortic ring, we have, nevertheless, experienced great difficulty in visualizing by study of the barium filled esophagus, all of the elements necessary to make a diagnosis accurate enough to assure a reliable surgical approach to its cure. In infants we sometimes have been unable to determine the position of the descending aorta because of the presence of mediastinal shift due to pulmonary disease; this positively must be ascertained before an anatomic diagnosis is possible. The apparent breadth and direction of abnormal filling defects in the esophagus have been used, often correctly, as criteria for establishing the identity of the retroesophageal vessel. This may be misleading. A deformity passing obliquely across the posterior aspect of the esophagus at the level of the aortic arch is probably caused by a retroesophageal subclavian artery, but an aortic arch passing posterior to the esophagus to reach a descending aorta on the opposite side may pass obliquely downward, rather than transversely across, to this junction. The apparent width of the compressed esophageal segment is of little value in this differential diagnosis, since a small vessel may produce an apparently large defect. This is well illustrated in figure 4. The defect in the esophagus appears to be as wide as the descending aorta, but was produced by the much narrower subclavian artery.

Keith and Forsyth[8] have recently shown the practicability of demonstrating the presence of coarctation of the aorta and patent ductus arteriosus in infants by retrograde aortography. We have utilized this technic in order to clarify some of the problems outlined previously, when preliminary study of the barium-filled esophagus has indicated the existence of a constricting anomaly of the aortic arch.

The method used has been essentially that described by Keith and Forsyth. General anesthesia has not been utilized. In infants premedication consisted of morphine sulfate gr. 1/64 and atropine sulfate gr. 1/1000 per 10 pounds of body weight. Adults were given the same medications in appropriate doses 30 minutes before the test.

The brachial artery opposite the apparent side of the descending aorta was selected. After local infiltration of the skin and periarterial tissues, an incision was made over the artery above the antecubital space, and the largest possible needle was introduced under direct vision. In infants an 18 gage or larger needle was used, and in adults a 12 gage cannula was employed. Injection of contrast substance was made into the artery as rapidly as possible. Both 35 and 70 per cent diodrast were used on different occasions. Immediately prior

to injection a swallow of barium was given to outline the course of the esophagus. X-rays have been taken in the posteroanterior view with the patient in the supine position in order to lateralize clearly the descending aorta in its relation to the esophagus. One and one-fourth cc. of diodrast per kg. of body weight was given to infants, and in adults the total dose varied between 30 and 40 cc.

Tight manual compression upon the carotid artery on the homolateral side at a level immediately above the clavicle was made during the moment of injection, to reduce the possibility of a large amount of dye passing directly into the cerebral circulation. Failure to do this resulted, on one occasion, in immediate syncope, accompanied by the clinical appearance of cardiac asystole of about 15 seconds' duration. No significant reaction occurred in any other patient when satisfactory carotid compression was accomplished. The possibility of introducing a large amount of dye into the cerebral circulation is greatest if the brachial artery used is derived from an innominate artery. In dealing with these anomalies one may not be certain of the location of the innominate artery, if one is present. We believe, therefore, that adequate carotid compression is essential during every injection.

Since we have been unable to expose x-ray films more rapidly than once per second, we have made a single exposure at the instant the injection was completed.

In all patients studied, this technic permitted adequate diagnosis for the determination of operability, and allowed selection of the best surgical approach to the lesion.

In every case the best surgical approach to the defect is from the side of the upper portion of the descending aorta. Posterolateral incision through the fourth interspace is chosen in the case of retroesophageal subclavian arteries. In this manner it is possible to mobilize the upper descending aorta below the level of the homolateral subclavian artery and to divide the anomalous vessel at its origin, thus allowing it to retract to the opposite side; this effectively relieves the esophageal compression.

In those instances in which the entire aortic arch, or the largest segment of a double aortic arch, passes posterior to the esophagus to reach the descending aorta on the opposite side, anterolateral approach on the side of the descending aorta is indicated. We doubt the value of operation in these cases unless organic occlusion of the trachea is demonstrated, since resection of the posterior arch cannot be performed to relieve esophageal compression. The only benefit to be anticipated from surgery is relief of tracheal occlusion.

In the uncommon event that a double aortic arch is demonstrated, in which the anterior arch on the side of the descending aorta is shown to be of equal or larger size than the posterior contralateral arch, division of the posterior arch may be accomplished by anterolateral approach on the side of the descending aorta. This will effectively relieve esophageal compression. Division of the posterior arch must be done distal to the origins of the homolateral carotid and subclavian arteries.

If symptoms in an infant are of mild degree, or if the defect is recognized

as inoperable, intelligent medical management will decrease morbidity and often insure survival. The frequency and magnitude of aspirations may be materially reduced by the simple expedient of restraining the infant on its abdomen during sleep and after feedings, with the head at a level slightly lower than the feet. This will facilitate drainage of regurgitated food and secretions. The mothers of such children must be taught the importance of slow and careful feeding, and bottle propping must be absolutely forbidden. Mothers must also be instructed in the recognition of the acute signs of aspiration and in the prompt institution of postural drainage should this occur.

If postural drainage does not result in rapid clearing of symptoms, skillful bronchoscopic drainage may be necessary. Penicillin is given prophylactically for 48 to 72 hours after any functionally significant aspiration, and materially reduces the incidence of postaspiration pneumonitis. It is often possible by the judicious use of these measures to support an infant through the earliest and most hazardous months of life; after the age of 2 years the outlook for survival is excellent.

Summary

1. A simple clinical classification of constricting anomalies of the aortic arch is presented, which has proved adequate for practical evaluation and treatment.

2. Retrograde aortography has been a useful technic for a more accurate diagnosis of these lesions. Its applicability is illustrated.

3. The indications for surgery and the selection of the best operative approach are discussed briefly.

4. Basic principles of medical management are outlined.

References

1. Edwards, J. E.: Anomalies of derivatives of aortic arch system. M. Clin. North America **32**:925 (July) 1948.
2. Griswold, H. E. and Young, M. D.: Double aortic arch. Pediatrics **4**:751 (Dec.) 1949.
3. Gordon S.: Double aortic arch. Arch. Pediat. **30**:428 (April) 1947.
4. Crystal, D. K., Edmonds, H. W. and Betzold, P. F.: Symmetrical double aortic arch. West. J. Surg. **55**:389 (July) 1947.
5. Arkin, A.: Double aortic arch with total persistence of right and isthmus stenosis of left arch; new clinical and x-ray picture. Am. Heart J. **11**:444 (April) 1946.
6. Neuhauser, E. B. D.: Roentgen diagnosis of double aortic arch and other anomalies of great vessels. Am. J. Roentgenol. **56**:1 (July) 1946.
7. Holzapfel, G., cited by Gross, R. E. and Ware, P. F.: Surgical significance of aortic arch anomalies. Surg., Gynec. and Obst. **83**:435 (Oct.) 1946.
8. Keith, J. D. and Forsyth, C.: Aortography in infants. Circulation **2**:907 (Oct.) 1950.

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

A Continuation course will be presented on
Thursday, Friday, and Saturday, November 15, 16, and 17, 1951

CURRENT THERAPY OF COMMON MEDICAL PROBLEMS

Tentative Program

Thursday, Nov. 15, 1951

8:00-8:50 a.m.	Registration	
8:50 a.m.	Orientation	A. C. ERNSTENE, M.D.
9:00 a.m.	Medical Management of Gastric and Duodenal Ulcers	E. N. COLLINS, M.D.
9:20 a.m.	Surgical Management of Gastric and Duodenal Ulcers	S. O. HOERR, M.D.
9:40 a.m.	Medical Care of Chronic Ulcerative Colitis	C. H. BROWN, M.D.
10:00 a.m.	Surgical Treatment of Ulcerative Colitis	R. B. TURNBULL, M.D.
10:20 a.m.	Diagnosis of Common Hepatic Diseases	H. R. ROSSMILLER, M.D.
10:45 a.m.	Intermission	
11:00 a.m.	Treatment of Hepatic Disease	CHESTER M. JONES, M.D.*
11:45 a.m.	Question and Answer Panel	
12:30 p.m.	Luncheon—Courtesy of Cleveland Clinic	
1:30 p.m.	Treatment of Rheumatic Fever	A. C. ERNSTENE, M.D.
1:50 p.m.	Prophylaxis of Rheumatic Fever and Bacterial Endocarditis	R. A. VAN OMMEN, M.D.
2:10 p.m.	Thromboangiitis Obliterans and Arteriosclerosis Obliterans	F. A. LEFEVRE, M.D.
2:30 p.m.	Spontaneous Subarachnoid Hemorrhage	W. J. GARDNER, M.D.
2:50 p.m.	Intermission	
3:00 p.m.	Thrombo-Embolic Disease	F. A. LEFEVRE, M.D.
3:20 p.m.	Clinical Use of Anticoagulants	V. G. DEWOLFE, M.D.
3:40 p.m.	Diagnosis and Treatment of Acute Coronary Insufficiency and Acute Myocardial Infarction	A. C. ERNSTENE, M. D.
4:20 p.m.	The Shoulder-Hand Syndrome	PAUL NELSON, M.D.
4:40-5:20 p.m.	Question and Answer Panel	
	Guest Speaker	
8:00 p.m.	Problems in Gastrointestinal Absorption	CHESTER M. JONES, M.D.

Friday, Nov. 16, 1951

8:00 a.m.	Medical Clinic	
9:00 a.m.	Management of Essential Hypertension	R. D. TAYLOR, M.D.
9:20 a.m.	Electrolyte and Fluid Balance	A. C. CORCORAN, M.D.
9:40 a.m.	Acute Renal Insufficiency	W. J. KOLFF, M.D.
10:00 a.m.	Diagnosis and Treatment of Pyelonephritis	D. C. HUMPHREY, M.D.
10:20 a.m.	Genesis of Arteriosclerosis and Role of Dietotherapy	I. H. PAGE, M.D.

*Clinical Professor of Medicine, Harvard University Medical School.

10:50 a.m.	Intermission	
11:00 a.m.	Diagnosis of Pheochromocytoma	HARRIET DUSTAN, M.D.
11:20 a.m.	Diagnosis of Coarctation of the Aorta	W. L. PROUDFIT, M.D.
11:40 a.m.	Treatment of Coarctation of the Aorta	D. B. EFFLER, M.D.
12:00-12:30 p.m.	Question and Answer Panel	
12:30 p.m.	Luncheon—Courtesy of Cleveland Clinic	
1:30 p.m.	Systemic Lupus Erythematosus	J. R. HASERICK, M.D.
1:50 p.m.	Pericarditis and Chronic Cardiac Tamponade	J. F. WHITMAN, M.D.
2:10 p.m.	Treatment of Pernicious Anemia and other Macrocytic Anemias	J. D. BATTLE, JR., M.D.
2:30 p.m.	Management of Asthma	C. R. K. JOHNSTON, M.D.
2:50 p.m.	Intermission	
3:00 p.m.	Treatment of Pneumonias	H. S. VAN ORDSTRAND, M.D.
3:20 p.m.	Management of Headache	L. L. LOVSHIN, M.D.
3:40 p.m.	Treatment of Syphilitic Aortitis	E. W. NETHERTON, M.D.
4:00 p.m.	Indications for/and Technic of Cardiac Catheterization	F. M. SONES, M.D.
4:20-5:00 p.m.	Question and Answer Panel	
5:30 p.m.	Cocktails—Courtesy of Cleveland Clinic	

Saturday, Nov. 17, 1951

9:00 a.m.	Diagnosis of Disease of the Thyroid Gland	George Crile, Jr., M.D.
9:30 a.m.	Medical Treatment of Thyrotoxicosis, Including Radioactive Iodine	E. P. MCCULLAGH, M.D.
10:00 a.m.	Indications for Surgical Treatment of Thyroid Disease	R. S. DINSMORE, M.D.
10:30 a.m.	Intermission	
10:45 a.m.	Parathyroid Disease and its Management	R. W. SCHNEIDER, M.D.
11:15 a.m.	Question and Answer Panel	

REGISTRATION BLANK

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Please register me for the course on "Current Therapy of Common Medical Problems" which is to be given November 15, 16, and 17, 1951. (Registration Fee is $15.00, except for members of the Armed Forces in uniform, interns and residents, who will be admitted free.)

I am enclosing check for $5.00 and the remainder will be paid on Registration, Nov. 15.

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Medical School and
date of graduation .....

This course is open only to graduates of approved medical schools. Registration will be limited to the number of physicians who can be accommodated adequately.

ANNOUNCEMENTS

A Postgraduate Course on "The Diagnosis and Treatment of Cardiovascular Disease" will be given at the Clinic under the auspices of the American College of Physicians from October 22 to October 27. The Course will place emphasis on current concepts of pathologic physiology and recent advances in the diagnosis and treatment of cardiovascular disease. The major forms of cardiac and peripheral vascular disease and their complications will be considered in detail, and there will be discussions also of less frequently encountered conditions. Newer knowledge in electrocardiography and roentgenologic diagnosis will be reviewed, and the surgical treatment of heart disease will be covered in several presentations. The Course will include lectures, clinical demonstrations, and question and answer panels.

Application should be made to Mr. E. R. Loveland, Executive Secretary, The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

Annual Lower Lecture

The William E. Lower Lecture will be given on November 16, 1951 at 8:30 p.m. at the Academy of Medicine in Cleveland. The lecturer this year will be Dr. William Boyd. Doctor Boyd is widely known as a speaker and as an author. His three books, Surgical Pathology, The Pathology of Internal Diseases and Textbook of Pathology have introduced him to a wide medical audience. Doctor Boyd, a graduate of the University of Edinburgh, was formerly Professor of Pathology at the University of Manitoba, until this summer Professor of Pathology at University of Toronto and now Professor of Pathology at the University of British Columbia. His subject will be:

"The Physiology and Pathology of Intercellular Substance"

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